IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS
EASTERN DIVISION

MELINTA THERAPEUTICS, LLC, MELINTA SUBSIDIARY CORP, and REMPEX PHARMACEUTICALS, INC.,

Plaintiffs,

v.

NEXUS PHARMACEUTICALS, INC.,

Defendant.

No. 21-cv-02636

Judge John F. Kness

FINDINGS OF FACT AND CONCLUSIONS OF LAW

This matter is before the Court for decision on the infringement and validity of Claims 1, 7, and 18 of the U.S. Patent No. 9,084,802 (the " '802 Patent") and Claim 27 of the U.S. Patent No. 9,278,105 (the " '105 Patent") (together, the "patents-in-suit"). The patents-in-suit cover the intravenous administration of Minocin® (minocycline) for injection ("Minocin") product, an aqueous solution consisting of minocycline and magnesium that is used to treat bacterial infections. The matter was before the Court for a bench trial over four days from June 6, 2023 to June 9, 2023. Closing arguments were heard separately on August 15, 2023. This is a Hatch-Waxman patent infringement action brought by Melinta Therapeutics, LLC; Melinta Subsidiary Corp.; and Rempex Pharmaceuticals, Inc. (together, the "Plaintiffs") against Nexus Pharmaceuticals, Inc. (the "Defendant"). It arises out of Defendant's filing of Abbreviated New Drug Application ("ANDA") No. 214934 containing a

Paragraph IV certification with the Food and Drug Administration ("FDA") seeking approval to market a generic version of Minocin identified in the ANDA.

Having considered the evidence presented during the bench trial, the parties' proposed findings of fact and conclusions of law, the relevant authorities, and the record as a whole, the Court finds that Plaintiffs have shown by a preponderance of the evidence that Defendant infringed on the asserted claims (the "Asserted Claims") in the patents-in-suit, and Defendant has failed to show by clear and convincing evidence that the Asserted Claims of the patents-in-suit are invalid for obviousness, indefiniteness, inadequate description, or lack of enablement. The Asserted Claims of the patents-in-suit are valid and enforceable. For the reasons set forth below, judgment is entered in favor of Plaintiffs and against Defendant, and a permanent injunction shall be entered accordingly.

In support of this decision, the Court makes the following findings of fact and conclusions of law under Rule 52 of the Federal Rules of Civil Procedure. Because the parties raised claim construction disputes on the first day of trial, this Memorandum also construes the several disputed claims. To provide clarity on the disputed claims, the Court begins with some findings of fact (Part II), detours with claim construction (Part III), finishes its findings of fact by describing the evidence the parties presented at trial (Part IV), and concludes with conclusions of law (Part V).

I. LEGAL STANDARD

In a bench trial "tried on the facts without a jury . . . , the court must find the facts specially and state its conclusions of law separately." Fed. R. Civ. P. 52(a)(1).

The primary purpose of Rule 52(a)(1) is to "aid[] the trial court's adjudication process by engendering care by the court in determining the facts." *Garner v. Kennedy*, 713 F.3d 237, 242 (5th Cir. 2013); *see also McKee v. Brunswick Corp.*, 354 F.2d 577, 580 (7th Cir. 1965). The trial court "need only make brief, definite, pertinent findings and conclusions upon the contested matters" such that the findings are "explicit enough to enable appellate courts to carry out a meaningful review." Fed. R. Civ. P. 52(a)(1) advisory committee's note to 1946 amendment; *Garner*, 713 F.3d at 243.

II. FINDINGS OF FACT

A. The Parties and Procedural Posture

Plaintiffs are biopharmaceutical companies that develop antibiotics to treat infectious diseases. (Dkt. 252 ¶ 4.) Plaintiffs own New Drug Application No. 050444 (the "NDA") for the FDA-approved Minocin product. (Dkt. 228-1 ¶ 5.) Plaintiffs own the '105 Patent and the '802 Patent, which are both listed in the FDA's Orange Book[1] in connection with the NDA and Minocin. (Dkt. 228-1 ¶¶ 7, 16–17, 26–27.) The inventors of the patents-in-suit are David C. Griffith, Serge Boyer, Scott Hecker, and Michael N. Dudley. (*Id.* ¶¶ 9, 20.) The priority date of the patents-in-suit is May 12, 2010. (*Id.* ¶¶ 8, 19.)

Defendant Nexus Pharmaceuticals, Inc. is a pharmaceutical company that makes generic versions of FDA-approved injectable drug products. (Dkt. 252 ¶ 7.)

[1] The "Orange Book" is a publication authored by the FDA that "identifies drug products approved on the basis of safety and effectiveness [by the FDA] under the Federal Food, Drug, and Cosmetic Act . . . and related patent and exclusivity information." *Approved Drug Products with Therapeutic Equivalence Evaluations—Orange Book: Background*, U.S. Food & Drug Admin. (Jan. 25, 2024), https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book.

Defendant owns the ANDA, which Defendant submitted to the FDA on October 16, 2020 seeking to develop a generic version of Minocin prior to the expiration of the patents-in-suit. (Dkt. 228-1 ¶ 6.) As part of the ANDA approval process, Defendant sent a notice to Plaintiffs asserting that its ANDA did not infringe the patents-in-suit, or, alternatively, that the patents-in-suit were invalid. (*Id.*) Plaintiffs responded to the notice by filing this lawsuit, which triggered an automatic thirty-month stay[2] of regulatory approval of Defendant's ANDA. *See* 21 U.S.C. § 355(j)(5)(B)(iii).

Plaintiffs filed this lawsuit on May 14, 2021. (Dkt. 1.) On December 7, 2021, this case was consolidated with related Case No. 21-cv-05995, which was originally filed in the District Court for the District of New Jersey and transferred to this Court on November 5, 2021. (Dkts. 42; 45.) The related case asserts the same claims against Defendant and was, therefore, consolidated to save judicial time and resources. (Dkt. 42.) The cases were consolidated for pretrial and trial matters but were not merged, thereby requiring separate judgments. (Dkt. 45.)

Plaintiffs' complaint contains three counts. (Dkt. 1.) Count I, brought under 21 U.S.C. § 335(j)(5)(B)(iii) and 21 C.F.R. § 314.95, seeks a declaratory judgment to resolve whether the thirty-month stay of FDA approval was triggered. (*Id.* ¶¶ 1, 28–38.) Counts II and III were brought under 35 U.S.C. § 271(e)(2)(A), alleging that Defendant infringed upon the patents-in-suit when Defendant submitted its ANDA seeking approval to engage in the commercial manufacture, sale, use, and/or importation of Defendant's ANDA products before Plaintiffs' patents had expired. (*Id.*

[2] The stay ended on September 30, 2023. (Dkt. 228 ¶¶ 89–90.)

¶¶ 39–62.) Count II alleges infringement of the '105 Patent and Count III alleges infringement of the '802 Patent. (*Id.* ¶¶ 40, 52.) Defendant filed an answer and counterclaims. (Dkt. 9.) Defendant argues in Count I of the counterclaim that it did not infringe on the '105 Patent because the patent was invalid. (*Id.* ¶¶ 27–31.) Defendant makes identical arguments in Count II of the counterclaim, but for the '802 Patent. (*Id.* ¶¶ 32–36.)

Defendant moved to dismiss Count I of the complaint for lack of subject matter jurisdiction, or, alternatively, for failure to state a claim or under the doctrine of primary jurisdiction. (Dkt. 39.) This motion was stayed pending resolution of a related action in the District of Columbia. (Dkt 189; Dkt. 192.) *Melinta Therapeutics, LLC v. FDA*, No. 22-2190, 2022 WL 610018 (D.D.C. Oct. 7, 2022). In that case, the court granted Melinta's motion for a temporary restraining order and preliminary injunction, vacated the FDA's approval of the ANDA, and remanded the case to the FDA. *Melinta*, 2022 WL 610018, at *10. Defendant appealed this decision, but the District of Columbia Circuit dismissed the appeal for lack of jurisdiction and agreed that the case should remain remanded to the FDA. *Melinta Therapeutics, LLC v. FDA*, No. 22-5288, 2022 WL 19723218, at *1 (D.C. Cir. Dec. 1, 2022). The parties have since reported that the FDA has approved the ANDA. (Dkt. 271.) Accordingly, Count I is dismissed as moot. Counts II and III of Plaintiffs' complaint, along with Counts I and II of Defendant's counterclaims, proceeded to trial.

A bench trial took place over four days from June 6, 2023 to June 9, 2023. Closing arguments were heard separately on August 15, 2023. Plaintiffs called three

witnesses: (1) Dr. Bruce Friedman ("Dr. Friedman"), (2) Dr. Tina deVries ("Dr. deVries"), and (3) David Griffith ("Griffith"). (Dkt. 228¶ 16.) Defendant called two witnesses: (1) Dr. Henry F. Chambers ("Dr. Chambers"), and (2) Dr. Alexander Klibanov ("Dr. Klibanov"). (Dkt. 228 ¶ 18.) After Plaintiffs rested their case, Defendant moved for an oral Rule 52(c) judgment on partial findings in its favor. (Tr. 455:14–16.) The Court took the oral motion under advisement and reserved ruling until the close of evidence. (Tr. 456:3–21.) *See* Fed. R. Civ. P. 52(c). The Rule 52(c) motion is subsumed with the Court's following evaluation of the case.

After the conclusion of the bench trial, the parties submitted proposed findings of fact and conclusions of law with citations to the record. (Dkts. 252; 253; 255.) Because the issue of claim construction arose during the bench trial, both parties' proposed findings of fact and conclusions of law include their proposed constructions of several disputed claim terms within the allegedly infringing claims. (Dkt. 252 ¶¶ 45–91; Dkt. 255 ¶¶ 20–41.) The Court begins by first explaining the prior art minocycline, Minocin, and the ANDA product, and then reciting the disputed claims. With an understanding of the products at issue, the Court construes the disputed claims in Part III.

B. Plaintiffs' Minocin Product

Plaintiffs' Minocin product replaced an old intravenous (IV) minocycline formulation (the "prior art minocycline"), a product approved in 1972 to treat bacterial infections caused by the Acinetobacter baumannii bacteria. (Tr. 75:17, 322:17–323:14; DTX-0027.) The prior art minocycline was removed from the market

in 2005 but returned in 2009 because no other similar product existed to treat bacterial infections. (Tr. 705:8–10, 707:13–708:1.) Around that time, the inventors began research for the patents-in-suit, hoping to improve the prior art minocycline. (Tr. 320:9–22.) A few years later, Plaintiffs acquired the NDA for the prior art minocycline and shortly thereafter filed a supplemental NDA seeking to replace the prior art minocycline with their new Minocin formulation. (Dkt. 255 ¶¶ 10–11; DTX-0072.)

Both the prior art minocycline and Minocin are intended to be administered to a patient intravenously, *i.e.*, injected into the patient's vein. An intravenous product begins as a powder or other dried substance. But to be administered intravenously, the powder must be dissolved to create an aqueous[3] solution. Both the prior art minocycline and Minocin require dissolution—or, in scientific terms, reconstitution—in 5 mL of sterile water. (*See* DTX-110; DTX-112.) The reconstituted liquid solution is then a fully dissolved aqueous solution suitable for intravenous injection. Accordingly, the term "reconstituted solution" used in this Memorandum refers to the drug product dissolved in 5 mL of water before it is further diluted. After reconstitution, the reconstituted solution must be diluted further with an additional diluent to prepare it for intravenous administration. The prior art minocycline label instructs a POSA to further dilute the reconstituted solution in 500 mL to 1,000 mL of a compatible diluent. (DTX-112.) The Minocin label instructs further dilution in 100 mL to 1,000 mL of specific diluents, but the relevant claims in this action instruct

[3] "Aqueous" means "of the nature of water." Aqueous, *Taber's Medical Dictionary Online* (24th ed.).

an injection volume of "less than 500 mL." (DTX-110; PTX-1.) The diluted solution is also referred to as the "admixture."

The inventors of the patents-in-suit set out to improve the prior art minocycline. Although the prior art minocycline effectively treated bacterial infections, it suffered from several faults. First, it had a low pH level. Second, it required a high injection volume. Although Defendant disputes this, the low pH level and high injection volume created a risk of irritability, tolerability, and other injection site hemolysis[4] issues.

First, the prior art minocycline had a low pH level. A pH level is a "measure of acid intensity," and the lower the pH level, the more acidic a solution is. (Tr. 611:7–8.) The prior art minocycline pH levels range from 2.0 to 6. The pH level for the reconstituted solution is 2.0 to 2.8, 2.5 to 4 after dilution, and 4.5 to 6 after dilution in a particular diluent called Lactated Ringer's. (Tr. 328:25–329:5, 480:10–481:3, 611:9–18, 797:18–20, 890:8–17; DTX-112.) Dr. Friedman testified that those prior art minocycline pH levels were low, and that a pH level closer to 7.35 to 7.45 is needed for safe administration to patients. (Tr. 117:7–13.) A pH level that is too low—and therefore more acidic—can trigger injection site hemolysis. (*Id.* at 117:14–20, 117:25–118:14.)

Second, the prior art minocycline required a high injection volume. The prior art minocycline instructed an administration at a volume of at least 500 mL and up to 1,000 mL per infusion. A higher volume was required because more diluent

[4] The definition of "injection site hemolysis" follows in Section III.C.4 of this Memorandum.

increased the pH level and thus reduced injection site hemolysis. (*Id.* at 119:10–12, 323:25–324:7.) But a high infusion volume would put patients at risk of fluid overload, especially those patients who were already receiving other intravenous fluids. An overload of intravenous fluids then created a risk of other serious medical issues. (*Id.* at 118:15–19:9, 331:2–18.)

These issues caused the prior art minocycline to be used as a last resort before being removed from the market entirely. (Dkt. 252 ¶ 182; Tr. 704:18–05:15.) The product was reintroduced to the market a few years later because no other efficacious product existed to treat bacterial infections, but it continued to suffer from the same problems. Attempts to improve the prior art minocycline were "valiant" but ultimately unsuccessful due to solubility,[5] stability,[6] or injection site tolerability issues. (Dkt. 252 ¶ 183; Tr. 325:7–20, 709:17–710:14, 798:14–22.) Solubility was a problem because an intravenous product must be administered as an aqueous solution, and if the product is not completely dissolved, it cannot be intravenously administered safely. Stability was a problem because the minocycline molecule needs to remain unchanged to be effective against the bacteria it is intended to treat. And injection site tolerability issues were a problem because the aqueous formulation needed to be administered intravenously without causing harmful effects to the skin or the blood cells.

[5] "Solubility" refers to the "capability [of a substance] of being dissolved," a necessary property of all drugs in order for them to be administered to a patient. Solubility, *Taber's Medical Dictionary Online* (24th ed.). (*See also* Tr. 197:20–198:12.)

[6] "Stability" refers to "the condition of remaining unchanged, even in the presence of forces that would normally change the state or condition." Stability, *Taber's Medical Dictionary Online* (24th ed.). (*See also* Tr. 332:19–333:6.)

The inventors thus set out to improve the prior art minocycline without any solubility, stability, or tolerability issues. The final patented Minocin product differs from the prior art minocycline in one primary respect: the addition of magnesium. The addition of magnesium at a high ratio in relation to minocycline enables the pH of the solution to be adjusted to a more physiologic[7] range. In turn, if the pH can be adjusted higher, a high injection volume can be decreased because it is no longer needed to improve pH, thereby reducing injection site tolerability issues. (Tr. 121:18–23.) The pH levels for Minocin, according to its label, are as follows: 4.5 to 5.0 for the reconstituted solution, and 4.5 to 6 after dilution in compatible solutions. (DTX-110.) The injection volume for Minocin is 100 mL to 1,000 mL when diluted in various solutions, or 250 mL to 1,000 mL when diluted in Lactated Ringer's. (*Id.*)

The patents-in-suit elaborate on what the Minocin label states. They describe the use of minocycline (a 7-dimethylamino-tetracycline) with divalent[8] metal cations[9]. (Tr. 421:9–19; PTX-1; PTX-2.) The particular divalent metal cation specified in the patents-in-suit is magnesium. (*Id.*) The patents-in-suit specify that a higher molar ratio of divalent cations (specifically, magnesium) to a tetracycline (specifically,

[7] "Physiologic" means "characteristic of or appropriate to an organism's healthy or normal functioning." So, the characteristics of solution at a physiologic range are characteristics that match or are similar to those characteristics within an organism such as a human. Physiologic, *Mirriam-Webster Unabridged Dictionary*.

[8] "Divalent" describes the property of a molecule "having an electric charge of two." Divalent, *Taber's Medical Dictionary Online* (24th ed.).

[9] A "cation" is an "ion with a positive electric charge." Cation, *Taber's Medical Dictionary Online* (24th ed.). When used in the context of patient care, a cation is "a positively charged ion[] that contribute[s] to the pH of human plasma." *Id.* Examples of such cations are calcium, magnesium, potassium, and sodium. *Id.*

minocycline) successfully decreases hemolysis in relation to a formulation like the prior art minocycline that does not have magnesium. (*Id.*) The '802 Patent instructs a molar ratio of magnesium to minocycline that is greater than about 4 to 1, and the '105 Patent one that is greater than 3 to 1. (Tr. 107:15–108:2, 424:13–17; PTX-1 at 40:51–52; PTX-2 at 41:40.)

In addition, the '105 Patent specifies one additional property in its Minocin product. In Claim 1, the patent specifies "an osmolality[10] of less than about 500 milliosmols per kilogram (mOsmol/kg)." (PTX-002 at 41:43.) Osmolality is a measurement that can be calculated by a POSA after reading the ingredients and amounts of those ingredients on a product label. Neither the prior art minocycline label nor the Minocin label specify the osmolality level of their respective products.

C. Defendant's ANDA

Defendant filed its ANDA on October 16, 2020 seeking approval to develop a generic magnesium-based minocycline product before the expiration of the patents-in-suit, certifying that the patents-in-suit were either invalid or not infringed by the ANDA. (Dkt 228-1 at 1.) Because Minocin is an intravenous product, FDA regulations require generic products such as Defendant's ANDA to have the same active and inactive ingredients in the same amounts as Minocin. (Tr. 205:21–206:5.) The ANDA

[10] "Osmolality" refers to the "concentration of a solution expressed in osmoles of solute particles per kilogram of soluent." Osmolality, *Stedmans Medical Dictionary* (2014). Another medical dictionary defines "osmolality" as the "concentration of an osmotic solution by the concentration of the dissolved substances per 100 g [or 1 kg] of solvent." Osmolality, *Taber's Medical Dictionary Online* (24th ed.). In other words, osmolality measures (by weight) the concentration of dissolved particles in a solvent. (*See* Tr. 135:22–24.) The general standard of care for osmolality with respect to IV medications is less than 500 mOsmol/kg. (Tr. 136:15–18, 762:16–19.) A higher osmolality may cause tissue damage. (Tr. 137:10–12.)

describes a minocycline for injection product that contains three ingredients: (1) minocycline, (2) magnesium, and (3) a base. (PTX-042.) Defendant explained in several statements to the FDA that the purpose of magnesium in its ANDA product is reduction of injection site hemolysis. (Tr. 230:9–231:9; *see, e.g.*, PTX-021; PTX-206; PTX-211.) The ANDA does not identify a diluent in the list of ingredients. (*Id.*) But the ANDA label instructs that the composition be diluted in 100 to 1,000 mL of a diluent for adult use. (PTX-042.) According to the ANDA's label, the pH level of the ANDA composition before dilution is 4.5 to 5. (PTX-028; PTX-042.) After dilution, the pH "usually ranges from 4.5 to 6.0." (PTX-042.) The label does not specify the ANDA product's molar ratio or osmolality. The label explains that the ANDA minocycline for injection product is designed with the preceding ingredients and properties for the purpose of treating or preventing bacterial infections. (PTX-042.)

D. The Asserted Claims

1. The '802 Patent

Plaintiffs first assert infringement of Claims 1, 7, and 18 of the '802 Patent. (Dkt. 228-1 ¶ 12.) Claim 1 of the '802 Patent recites:

> 1. A method of treating a bacterial infection in a subject, wherein the method consists of:
>
> administering a therapeutically effective amount of a composition to a subject in need thereof via an intravenous route of administration,
>
> wherein the composition consists of an aqueous solution consisting of minocycline or a salt thereof, a salt that comprises a magnesium cation, and a base,
>
> wherein the molar ratio of magnesium cation to minocycline is greater than about 4:1, and

> wherein the composition has a pH that is no less than 4 and no greater than 6,
>
> whereby injection site hemolysis of red blood cells is reduced relative to intravenous administration of a composition that does not include magnesium.

(*Id.* ¶ 13.)

Claim 7 of the '802 Patent depends from Claim 1 and recites: "7. The method of Claim 1, wherein the composition has a pH between about 4.5 to about 5.5." (*Id.* ¶ 14.)

Claim 18 of the '802 Patent depends from claim 1 and recites: "18. The method of claim 1, wherein the total volume of the composition administered is less than 500 mL." (*Id.* ¶ 15.)

2. The '105 Patent

Plaintiffs next assert infringement of Claim 27 of the '105 Patent, which depends from Claim 1 of the '105 Patent. (*Id.* ¶ 23.) Claim 27 recites: "27. The method of claim 1, wherein the 7-dimethylamino-tetracycline is minocycline." (*Id.* ¶ 25.)

Claim 1 is an unasserted claim, but for clarity, because Claim 27 depends from it, Claim 1 recites:

> 1. A method of treating a bacterial infection in a subject, wherein the method comprises administering a therapeutically effective amount of a composition to a subject in need thereof via an intravenous route of administration, wherein the composition comprises an aqueous solution of a 7-dimethylamino-tetracycline antibiotic and a magnesium cation, wherein the molar ratio of magnesium cation to 7-dimethylamino-tetracycline antibiotic is greater than 3:1 and wherein the solution does not comprise a pharmaceutically acceptable oil, has a pH greater than 4 and less than 7, and has an osmolality less than about 500 mOsmol/kg.

(*Id.* ¶ 24.)

III. CLAIM CONSTRUCTION

The claims of a patent are questions of law to be determined by the district court, not a question of fact to be determined by the factfinder. *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 384 (1996). This process, dubbed "claim construction," is the "process of giving proper meaning to the claim language" which then "defines the scope of the protected invention." *Abtox, Inc. v. Exitron Corp.*, 122 F.3d 1019, 1023 (Fed. Cir. 1997). Claim construction "frames and ultimately resolves all issues of claim interpretation." *Id.*

The court typically construes claims and terms within claims before trial, after the parties submit claim construction briefs and the court conducts a claim construction hearing. *See* N.D. Ill. L. Pat. R. 4.1–4.3. But the court's understanding of claims may change as the trial proceeds. The court can thus engage in "rolling" claim construction, "in which the court revisits and alters its interpretation of the claim terms as its understanding of the [case] evolves." *Conoco, Inc. v. Energy & Env't Int'l, L.C.*, 460 F.3d 1349, 1359 (Fed. Cir. 2006) (quoting *Guttman, Inc. v. Kopykake Enters., Inc.*, 302 F.3d 1352, 1361 (Fed. Cir. 2002)).

On March 21, 2022, over one year before the bench trial was held, the parties filed a joint status report stating that "neither Plaintiffs nor Defendant identified any terms requiring construction. Accordingly, the parties agree that no briefing, hearing or claim construction ruling by the Court is necessary." (Dkt. 70 at 1–2.) But on June 6, 2023, the first day of the bench trial, Defendant informed the Court of a claim construction issue that arose the previous day that was "significant enough to raise"

at trial. (Tr. 3:13–19.) Defendant stated that after reviewing Plaintiffs' materials, it believed "plaintiffs intend to change the words or add to the words in the claim." (Tr. 4:8–12.) Plaintiffs denied that they were "arguing or proffering a special meaning of any of the claims," nor were they "attempting to add words to the claim." (Tr. 4:18–21.) The Court decided, with the parties' input and approval, to move forward with the trial, listen to the arguments, and determine after trial whether any claim construction issue persisted. (Tr. 7:17–10:3.) The parties were instructed to object during trial when a claim construction issue arose and file a post-trial motion or brief regarding the claim construction dispute if they deemed it necessary. (Tr. 7:17–10:3.) Both made claim construction objections during trial and presented various claim construction arguments in post-trial briefings. (Dkts. 249; 250; 251; 252; 253; 254; 255.) Accordingly, this Court must engage in post-trial rolling claim construction and will construe the several disputed claims raised by the parties.

A. Legal Standard

Claim construction begins with a "heavy presumption" that words in a claim are given their "ordinary and customary meaning." *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1327 (Fed. Cir. 2002); *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). The "ordinary and customary meaning" of a claim term is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention . . . ." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005). The court stands in the shoes of a person of ordinary skill in the art (a "POSA") and "review[s] the same resources as would" a POSA. *Multiform*

Desiccants, Inc. v. Medzam, 133 F.3d 1473, 1477 (Fed. Cir. 1998). The court, acting as a POSA, reads the claim terms "with an understanding of their meaning in the field" and applies "knowledge of any special meaning and usage [of the terms] in the field." *Phillips*, 415 F.3d at 1313.

Often, the ordinary and customary meaning of a claim term, even when read from the perspective of a POSA, is "readily apparent" and can be determined with "little more than the application of the widely accepted meaning of commonly understood words." *Id.* at 1314. In more complex cases, however, "because the meaning of a claim term as understood by [a POSA] is often not immediately apparent, and because patentees frequently use terms idiosyncratically, the court looks to" other sources to define the claim. *Id.* The court primarily looks to intrinsic evidence contained in the record, such as the claims themselves, the patent's specification, and the patent's prosecution history. *Id.*

The patent's claims themselves, along with the context in which the terms appear in the claim, "provide substantial guidance as to the meaning of particular claim terms." *Id.*; *ACTV, Inc. v. Walt Disney Co.*, 346 F.3d 1082, 1088 (Fed. Cir. 2003). Second, the patent's specification is "highly relevant" because new patents are required to be described in "full, clear, concise, and exact terms." *Vitronics*, 90 F.3d at 1582; 35 U.S.C. § 112. Accordingly, the construction "that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction." *Renishaw PLC v. Marposs Societa' per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998). An exception to this "ordinary and customary

meaning" rule exists when the inventor acts as the patent's lexicographer and expresses in the specification that a claim term has "a special definition . . . that differs from the meaning it would otherwise possess." *Phillips*, 415 F.3d at 1316. In such a circumstance, the inventor's definition is dispositive. *Id.* Third, the patent's prosecution history, which includes the "complete record of the proceedings before the [United States Patent and Trademark Office ("USPTO")] and includes the prior art cited during the examination of the patent," is helpful to claim construction because it provides insight into how the USPTO and inventor understood the patent and accurately represents what the patentee intended with the patent. *Id.* at 1317.

District courts are also authorized to look to extrinsic evidence such as dictionaries, treatises, and expert testimony to determine the "ordinary and customary meaning" of a claim term. *See id.* at 1317–18 (quoting *Markman*, 52 F.3d at 980). But the use of extrinsic evidence should be limited. Extrinsic evidence may not contradict the intrinsic evidence. *See Helmsderfer v. Bobrick Washroom Equip., Inc.*, 527 F.3d 1379, 1382 (Fed. Cir. 2008). Because extrinsic evidence is removed from the facts of the patent in question, it is less reliable than intrinsic evidence; extrinsic evidence should therefore only be "considered in the context of the intrinsic evidence." *Phillips*, 415 F.3d at 1319.

B. Person of Ordinary Skill in the Art

Because patent claims are construed from the perspective of a POSA, the Court must begin its claim construction analysis by defining who a POSA is in this case. A POSA is a hypothetical person "deemed to read the words used in the patent

documents with an understanding of their meaning in the field, and to have knowledge of any special meaning and usage in the field." *Id.* at 1313 (citing *Multiform Desiccants, Inc.*, 133 F.3d at 1477). A POSA is presumed to be aware of all pertinent prior art, regardless of whether the patentee is actually aware of the existence of all prior art. *See Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985).

The parties disagree slightly on the proper definition of a POSA. Plaintiffs' expert Dr. deVries testified that a POSA is "a chemist, a formulator, a pharmaceutical scientist or infectious disease or critical care doctor with an advanced degree and experience with chemistry, formulation, and / or administration of tetracyclines [who] . . . would collaborate with other POSAs as necessary." (Tr. 203:22–204:3.) Defendant's expert Dr. Klibanov testified that a POSA is an "individual with an advanced degree in pharmacy, chemistry, or a related field, plus practical experience with pharmaceutical formulations, including their methods of preparation, stability, characterization, and administration, along with a physician or a medical professional who administers injectable formulations." (Tr. 463:11–17.) The key difference between these proposed definitions is whether the POSA has experience working with tetracyclines. Both experts, however, stated that their opinions would not change if they applied the opposing party's definition of a POSA. (Tr. 204:8–11, 464:3–5.) Accordingly, this Court defines a POSA in this case with elements that are common to both parties: "an individual with an advanced degree in chemistry,

pharmacy, or a related field, and with experience in pharmaceutical formulations and administrations."

C. The Disputed Claim Terms

1. "Composition"

The parties first dispute the claim term "composition." This claim term appears multiple times in Claim 1 of the '802 Patent, which reads (with the relevant claim term underlined):

> 1. A method of treating a bacterial infection in a subject, wherein the method consists of:
>
> administering a therapeutically effective amount of a composition to a subject in need thereof via an intravenous route of administration,
>
> wherein the composition consists of an aqueous solution consisting of minocycline or a salt thereof, a salt that comprises a magnesium cation, and a base,
>
> wherein the molar ratio of magnesium cation to minocycline is greater than about 4:1, and
>
> wherein the composition has a pH that is no less than 4 and no greater than 6,
>
> whereby injection site hemolysis of red blood cells is reduced relative to intravenous administration of a composition that does not include magnesium.

The claim term also appears in Claims 7 and 18 of the '802 Patent, which depend on claim 1. Claim 7 reads: "The method of claim 1, wherein the composition has a pH between about 4.5 to about 5.5." Claim 18 reads: "The method of claim 1, wherein the total volume of the composition administered is less than 500 ml." Claim 27 of the '105 Patent also includes the word "composition," because it depends on Claim 1. Claim 27 reads: "The method of claim 1, wherein the 7-dimethylamino-tetracycline is minocycline." And Claim 1 reads:

> 1. A method of treating a bacterial infection in a subject, wherein the method comprises administering a therapeutically effective amount of a composition to a subject in need thereof via an intravenous route of administration, wherein the composition comprises an aqueous solution of a 7-dimethylamino-tetracycline antibiotic and a magnesium cation, wherein the molar ratio of magnesium cation to 7-dimethylamino-tetracycline antibiotic is greater than 3:1 and wherein the solution does not comprise a pharmaceutically acceptable oil, has a pH greater than 4 and less than 7, and has an osmolality less than about 500 mOsmol/kg.

In their post-trial briefings, Plaintiffs extensively argue that the plain and ordinary meaning of "composition" is the concentrated, reconstituted solution in the vial prior to dilution. (Dkt. 249 at 3.) Plaintiffs explain that everywhere the term "composition" is mentioned in the claims, it is in reference to the solution before dilution. (*Id.*; Dkt. 251 at 3–4.) In one place, "composition" is followed by a list of ingredients, none of which are a diluent. (Dkt. 249 at 3.) It follows, then, according to Plaintiffs, that "composition" includes only the listed ingredients before a diluent is added. (*Id.*) Plaintiffs' expert witnesses testified at trial that a POSA would agree, based on the patent's specification, that "composition" refers to the reconstituted solution before dilution. (Tr. 103:2–19; 217:19–218:10, 19–24.) In post-trial briefings, Plaintiffs emphasize that it is undisputed that the Asserted Claims are specific only to minocycline "compositions"—not all "compositions" in the specification—and the references to minocycline compositions in the specification do not include a diluent. (Dkt. 251 at 3–4.) Plaintiffs also cite the pH levels stated in the patents as further support for their proposed construction of "composition," arguing that all references to the pH of the "composition" in the patent specifications is to the pH levels of the reconstitute solution before adding a diluent. (Dkt. 249 at 4; Dkt. 252 ¶¶ 46–49.)

Defendant disagrees. Defendant argues that the plain and ordinary meaning of "composition" is whatever is administered to a patient. (Dkt. 250 at 16; Dkt. 254 at 8–10.) Defendant cites the patent specifications, which state that "composition" refers to what is administered—and because the solution can only be administered *after* it is diluted, "composition" must mean the diluted solution. (*Id.*)

The Federal Circuit has long viewed the term "composition" as a term of art in chemistry and patent law and has regularly interpreted a chemical "composition" to exist "at the moment the ingredients are mixed together. Before the creation of the mixture, the ingredients exist independently." *Exxon Chem. Patents, Inc. v. Lubrizol Corp.*, 64 F.3d 1553, 1558 (Fed. Cir. 1995). Consequently, a patentee's claims are a "composition that contains the specified ingredients at any time from the moment at which the ingredients are mixed together. This interpretation of [the patentee's] claims preserves their identity as product claims, and recognizes as a matter of chemistry that the composition exists from the moment created." *PIN/NIP, Inc. v. Platte Chem. Co.*, 304 F.3d 1235, 1244 (Fed. Cir. 2002) (quoting *Exxon*, 64 F.3d at 1558); *see also Mars, Inc. v. H.J. Heinz Co., L.P.*, 377 F.3d 1369, 1374 (Fed. Cir. 2004); *Kim v. The Earthgrains Co.*, 2005 WL 66071, at *11 (N.D. Ill. Jan. 11, 2005) (construing "composition" in the patent as the "specific ingredients . . . at any time from the moment they are mixed together").

Applying this standard, the plain and ordinary meaning of "composition" refers to the specified ingredients stated in the claim the moment they are mixed together. There are three specified ingredients in Claim 1 of the '802 Patent: "an aqueous

solution consisting of minocycline or a salt thereof, a salt that comprises a magnesium cation, and a base." (PTX 1 at 40:48–50.) And there are two specified ingredients in Claim 1 of the '105 Patent: "an aqueous solution of a 7-dimethylamino-tetracycline antibiotic and a magnesium cation." (PTX 2 at 41:37–48.) A diluent is not mentioned in either. The "composition" thus means the three ingredients specified in Claim 1 of the '802 Patent claims and the two ingredients specified in Claim 1 of the '105 Patent at the moment they are mixed, without a diluent.

The '802 Patent and '105 Patent specifications do not, as Defendant contends, provide a basis for deviating from this plain and ordinary meaning. The word "composition" is used many times throughout the specifications, but the Asserted Claims in the case are directed in particular to the minocycline "compositions" mentioned in the specifications. (Tr. 203:13–18.) The four minocycline compositions in the specifications do not include a diluent in the list of ingredients. (PTX-1 at 3:38–55; PTX-2 at 3:32–49.) Defendant cites to several places in the specifications that allegedly prove the existence of a diluent in the "composition," but the examples Defendant points to are not specifically minocycline "compositions," and they do not say anything about a diluent as an ingredient. (*See* Dkt. 250 at 16; PTX-1 at 6:26–36, 12:13–34.) None of the minocycline "compositions" in the specifications provide any basis for deviating from the plain and ordinary meaning of the phrase "composition." Defendant does not argue that the prosecution history suggests otherwise.

Based on this construction, the Court agrees with Plaintiffs that all references in the specifications to the pH of the composition describe the pH of the reconstituted

solution without a diluent. All pH references in the specifications follow an ingredient list (none of which include a diluent) or explicitly say that the stated pH level is "the pH of a reconstituted solution." (PTX-1 at 3:38–4:24, 14:46–15:56, 38:1–39:55; PTX-2 at 3:32–4:18, 14:32–15:42, 38:59–40:45.)

For these reasons, this Court holds that the term "composition" as used in Claims 1, 7, and 18 of the '802 Patent refers to the three ingredients—minocycline, magnesium, and a base—explicitly listed in the claims at the moment the ingredients have been mixed together. In Claims 1 and 27 of the '105 Patent, the claim term "composition" refers to the two ingredients—minocycline and magnesium—explicitly listed in Claim 1 at the moment the ingredients have been mixed together. It therefore follows that the pH level of the "composition" stated in the claims is the pH level of the reconstituted solution without a diluent.

2. "Consists / consisting of"

The second disputed claim term is "consists of" or "consisting of." This claim term is closely related to "composition." The terms are adjacent to one another in Claim 1 of the '802 Patent: " . . . wherein the composition consists of an aqueous solution consisting of minocycline or a salt thereof, a salt that comprises a magnesium cation, and a base . . . ." Like "composition," the parties dispute whether the claim term "consists / consisting of" includes a diluent.

Diverting from its position on the term "composition," Defendant argues that "consists / consisting of" *does not* include a diluent. Defendant argues that the claim

term "consists / consisting of" can only refer to the three ingredients that are listed in the patent (minocycline, magnesium cation, and a base). (Dkt. 250 at 16–18.)

Plaintiffs do not explicitly construe "consists / consisting of," and only mention the claim term in their post-trial briefings to respond to Defendant's proposed construction. Plaintiffs argue that Defendant's construction of "consists / consisting of" is at odds with its proposed construction of "composition." (Dkts. 249 at 5–6; 251 at 5–6.) It is Plaintiffs' position that Defendant's constructions of "composition" and "consists / consisting of" cannot both be correct. (Dkt. 251 at 5–6.) According to Plaintiffs, if Defendant is correct that "composition" *does* include a diluent, but "consists / consisting of" *does not* include a diluent, the patent could never be infringed—which "cannot be correct." (Dkts. 249 at 5–6; 251 at 5–6.)

Like "composition," the claim term "consists of" or "consisting of" is a well-established term of art in patent law. The Federal Circuit has repeatedly held that the phrase "consists of" or "consisting of" is generally understood to be a closed phrase that excludes any element, step, or ingredient not specified in the claim. *See Norian Corp. v. Stryker Corp.*, 363 F.3d 1321, 1331 (Fed. Cir. 2004) (" 'Consisting of' is a term of patent convention meaning that the claimed invention contains only what is expressly set forth in the claim."). *See also, e.g.*, *Shire Dev., LLC v. Watson Pharms., Inc.*, 848 F.3d 981, 984 (Fed. Cir. 2017); *Multilayer Stretch Cling Film Holdings, Inc. v. Berry Plastics Corp.*, 831 F.3d 1350, 1358 (Fed. Cir. 2016); *AFG Indus., Inc. v. Cardinal IG Co., Inc.*, 239 F.3d 1239, 1245 (Fed. Cir. 2001); *Ga.-Pac. Corp. v. U.S. Gypsum Co.*, 195 F.3d 1322, 1327–28 (Fed. Cir. 1999). This general presumption can

be overcome if the specification and prosecution history "unmistakably manifest an alternative meaning." *Shire Dev., LLC*, 848 F.3d at 984 (quoting *Multilayer Stretch*, 831 F.3d at 1359).

Claim 1 of the '802 Patent uses the phrases "consists of" and "consisting of" to list three ingredients in the composition. The ingredients listed in the claim are minocycline, magnesium, and a base. Applying the Federal Circuit's precedent, this Court construes "consists / consisting of" to mean those three ingredients and to exclude all other ingredients. Neither party argues that the specification or patent history manifests an alternative meaning.

This construction of both "composition" and "consists of / consisting of" is supported by the fact that, as Plaintiffs argue, an alternative claim construction construing "composition" to include a diluent and "consists / consisting of" to not include a diluent would render the claim incoherent and "nonsensical." (Dkt. 251 at 6.) *See Source Vagabond Sys. Ltd. v. Hydrapak, Inc.*, 753 F.3d 1291, 1301 (Fed. Cir. 2014). To simultaneously hold, as Defendant argues, that "composition" includes a diluent but that "consists / consisting of" does not include a diluent is inconsistent at best, because both terms describe the same list of ingredients. Such a construction also "renders the claimed invention inoperable," as it would be impossible for the invention to work, much less be infringed. *AIA Eng'g Ltd. v. Magotteaux Int'l S/A*, 657 F.3d 1264, 1278 (Fed. Cir. 2011) (quoting *Talbert Fuel Sys. Patents Co. v. Unocal Corp.*, 275 F.3d 1371, 1376 (Fed. Cir. 2002)). The Court views such a construction with "extreme skepticism" and thus rejects Defendant's construction. *Id.* at 1278.

These constructions are consistent with the language of the claims, the patents' specifications, and Federal Circuit precedent, and the Court is not "redrafting" these claim terms in coming to these conclusions, as Defendant suggests. (Dkt. 250 at 17–18.) *See Chef America, Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371, 1374 (Fed. Cir. 2004).

3. "Administering"

The parties next dispute the term "administering." The term "administering" is related to both "composition" and "consists / consisting of." The term is used once in Claim 1 of the '802 Patent to describe the method of using the composition: " . . . wherein the method consists of: administering a therapeutically effective amount of a composition to a subject in need thereof via an intravenous route of administration . . . ." (PTX 1.) The term is used similarly in Claim 1 of the '105 Patent: " . . . wherein the method comprises administering a therapeutically effective amount of a composition to a subject in need thereof via an intravenous route of administration . . . ." (PTX-2.) The parties' claim construction dispute with the term "administering" is, like "composition" and "consists / consisting of," whether the act of administering the composition includes dilution.

Although Plaintiffs construe "composition" to not include a diluent, Plaintiffs construe "administering" to mean delivering the "composition" to the patient with a diluent. (Dkt. 249 at 4; Dkt. 251 at 2–3.) Plaintiffs argue that since the claims "recite administering the composition intravenously," a POSA would recognize that "administering" the solution through an intravenous route is a "one-step process" involving the mixing of a diluent into the reconstituted solution to ready it for

intravenous administration to the patient. (Dkt. 249 at 4; Tr. 100:10–16, 102:12–103:1.) A POSA would know that the solution could not be administered intravenously by itself without a diluent. (Dkt. 249 at 4; Dkt. 251 at 3.) Accordingly, "administering" must involve a diluent; otherwise, the claim would describe an unusable product.

Elaborating on its construction of "consists / consisting of," Defendant argues that because its proposed construction of that claim term does not include a diluent, the claim term "administering" also does not involve a diluent. Defendant asserts that the term "administering" means the injection into a patient of the reconstituted solution without a diluent. (Dkt. 250 at 15–16.) Plaintiffs object to Defendant's construction of this term by pointing out Defendant's inconsistency in arguing that "composition" means the three ingredients plus a diluent, yet also arguing that "administering" the composition does not include a diluent (Dkt. 249 at 6.) Plaintiffs conclude that such a construction cannot be correct, because under Defendant's constructions of these claim terms, no one could ever possibly follow the patent's specification—therefore, infringement too would be impossible. (Dkt. 249 at 6.)

The word "administer" is a "[c]ommon English word" understood by any ordinary person. *ecoNugenics, Inc. v. Bioenergy Life Sci., Inc.*, 355 F. Supp. 3d 785, 795 (D. Minn. 2019). A lay judge can therefore easily conclude that the plain and ordinary meaning of the word is, in the medical sense, " 'to introduce into or ingest' a medication." *Id.* According to Miriam-Webster's unabridged dictionary, "administer" means "to give remedially (as in medicine)." *Administer*, Miriam-Webster Unabridged

Dictionary. That definition, in combination with the term as it is used in the patent claims, informs the Court that "administering" means "to give the composition remedially." The exact method, however, of "administering" the composition requires looking at the patent claims and specifications from the perspective of a POSA.

As to claim language, Claim 1 of the patents-in-suit specifies that the composition is to be administered "intravenously." (PTX-1; PTX-2.) The claims explain that the "administering" of the composition is for the purpose of "treating a bacterial infection." (*Id.*) The patent specifications, in turn, repeatedly specify that "administering" must be done "via an intravenous route" or "intravenously." (*Id.*) The specifications also explicitly discuss the addition of a diluent to prepare the solution for intravenous administration: "To prepare an admixture, sufficient reconstituted solution is mixed in an intravenous bag containing a pharmaceutically acceptable diluent." (PTX-2 at 13:23–42.) The specification continues, stating that once the reconstituted solution is mixed with a diluent, the "solution is ready for administration." (*Id.*; *see also* Tr. 219:6–22.)

That the composition is to be administered intravenously is an important consideration. It implies that the composition can be administered to a patient only by a POSA who knows how to administer medication intravenously. Exactly how a POSA would intravenously give the composition to a patient is therefore relevant. For example, in *Shire LLC v. Amneal Pharms.*, No. 11-3781, 2013 WL 4045622 (D.N.J. Aug. 8, 2013), the court held that the defendants' proposed construction of "administering" an oral medication did not mean "physically delivering into the body

of the patient" because the patents did not envision physical delivery of the medication to a patient by a physician. *Id.* at *17–19. That court noted that if the medication were one that was "given intravenously, there might be a case" for defendant's proposed construction. *Id.* at *17. This case is distinct from *Shire LLC* because the patents-in-suit do envision physical—specifically, intravenous—delivery of the composition into a patient. Accordingly, the Court must consider how a POSA is to safely deliver the composition to a patient intravenously.

At trial, the expert witnesses confirmed the method of intravenously administering the composition to treat a bacterial infection. Dr. Friedman testified that to use the composition, a POSA would "take th[e] reconstituted solution and mix it into an appropriate diluent, which will then be provided for intravenous administration to the patient." (Tr. 102:20–23.) He continued, confirming that the reconstituted solution must "be further diluted" before being administered to a patient. (Tr. 102:24–104:25; *see also id.* 436:23–437:6, 720:1–10.) Plaintiffs' second expert witness Dr. deVries then testified that the "admixture" of the composition plus a diluent "is what is administered or injected into the vein of the patient." (Tr. 219:21–22.) Defendant's expert witness Dr. Chambers testified on cross-examination that the composition could not be administered "in any way directly to a patient" without first being "further diluted in a diluent." (Tr. 675:8–676:4.) The testimony of these three expert witnesses strongly indicates that a POSA would understand that proper administration of the aqueous solution would require dilution of the composition before intravenously injecting it into a patient's vein.

The Court sympathizes with Defendant's argument for the exclusion of a diluent in administration, because the claim language in both patents does not mention a diluent. But with due respect to Defendant's position, the Court cannot agree that "administering" excludes a diluent. The intrinsic evidence demonstrates that the meaning of "administering" cannot begin and end with the words in these claims. First, the language of Claim 1 in the patents-in-suit states that the purpose of the claimed invention is to "treat[] a bacterial infection." The composition can only effectively treat a bacterial infection if diluted. Second, both the specifications and the claim language require the composition to be administered intravenously. The composition can only be intravenously administered to a patient if diluted. Third, the specifications contemplate the mixture of a diluent with the composition before intravenous administration. Fourth, the trial testimony of three expert witnesses (all of whom would qualify as a POSA) confirmed the necessity of diluting the composition before it can be safely administered to a patient. Examining this intrinsic and extrinsic evidence, this Court holds that diluting the composition is a necessary prerequisite to "administering" the composition and is therefore included in the construction of that claim. *See, e.g.*, *Hospira, Inc. v. Amneal Pharms., LLC*, 285 F. Supp. 3d 776, 803 (D. Del. 2018) (quoting *Phillips*, 415 F.3d at 1314) (although the claim language did not explicitly specify the storage condition of a pharmaceutical composition, the term "administration" included storage condition because "even a lay judge can recognize that proper storage of a pharmaceutical is a prerequisite to administering the pharmaceutical intravenously to a patient").

The Court's construction does not divert from the plain and ordinary meaning of the word "administering," which is, as stated earlier, "to give remedially." Indeed, the Court's construction still means "to give remedially." *Cf. ecoNugenics, Inc.*, 355 F. Supp. 3d at 795–96 (rejecting a proposal to construe "administer" as "make available," "provide," "market," or "sell" and instead construing the term in its "obvious and ordinary meaning" of "to introduce into or ingest" a medication). This construction merely recognizes that the composition cannot be given remedially to a patient consistent with the patent claims and specifications without the use of a diluent. A POSA would read the patent claims and specifications and know to add a diluent to the composition for safe and effective intravenous administration. In short, the composition can only be "given remedially"—or "administered"—intravenously if diluted. This conclusion is supported by the intrinsic and extrinsic evidence and does not divert from the plain and ordinary meaning of the word "administering." Accordingly, this Court holds that "administering" means "to remedially give the diluted composition to a patient via an intravenous route."

4. "Injection Site Hemolysis"

The parties also dispute the term "injection site hemolysis," which appears once in Claim 1 (and, therefore, in Claims 7 and 18) of the '802 Patent: "A method of treating a bacterial infection in a subject . . . whereby injection site hemolysis of red blood cells is reduced relative to intravenous administration of a composition that does not include magnesium." (PTX-1.)

Plaintiffs argue that the plain and ordinary meaning of "injection site hemolysis" is "damage to red blood cells . . . that is caused by intravenously administered formulations, which in turn causes a cascade of events that can clinically manifest near the injection site . . . in various ways including, for example, phlebitis (skin inflammation), erythema (redness), skin damage / necrosis, thrombophlebitis (swelling / clot in the vein), and pain." (Dkt. 249 at 7; Dkt. 252 ¶ 62–63.) Plaintiffs add that a "POSA would understand the 'injection site' region to be the area around or above where the intravenous port enters the skin and goes into the vein, and 'injection site hemolysis' also includes issues downstream due to blood flow." (Dkt. 249 at 7; Dkt. 252 ¶ 63.)

Plaintiffs argue that the '802 Patent's specification supports this definition. For instance, the specification states, "hemolysis can lead to venous phlebitis at the site of injection when administered intravenously, resulting in irritation . . . ." (Dkt. 249 at 7; Dkt. 252 ¶ 66.) A POSA would be able to recognize the signs and symptoms of injection site hemolysis and how to reduce the risk after reading the patent's specification. (Dkt. 249 at 7–8; Tr. 115:3–116:3.)

Defendant's view on the claim term "injection site hemolysis" is that it is indefinite and undefined. (Dkt. 254 at 10–11.) This view is stated through Dr. Klibanov's testimony: "the claim term 'injection site hemolysis' is somewhat vague, in that there is no teaching in the asserted patents how to measure it, how to know whether the injection site hemolysis is reduced or not." (Tr. 505:6–9.) Dr. Chambers agreed with this view, testifying that "injection site hemolysis" is not a defined term

in the medical field and does not have an agreed meaning across drug usage. (Tr. 595:2–597:8.) He added that "injection site hemolysis" is also not defined in the patent's specification, much less a method of determining or measuring its occurrence. (Tr. 596:21–597:8.)

Defendant accurately argues that "injection site hemolysis" is not a defined medical term. "Hemolysis" is a scientific term meaning the "destruction of red blood cells." *Hemolysis*, Taber's Medical Dictionary Online (24th ed.); *Hemolysis*, Stedmans Medical Dictionary. "Injection site" is a term a POSA would understand to mean the region around or above where the intravenous port enters the skin and goes into the vein. (*See* Tr. 113:24–115:17, 696:5–25.) But the term "injection site hemolysis" is not one with a "plain and ordinary meaning" in the medical field. Accordingly, the Court will turn to the '802 Patent's claim language and specification to determine the plain and ordinary meaning of the claim term.

The claim language only mentions "injection site hemolysis" once, to explain that the method in the claimed invention reduces injection site hemolysis "relative to intravenous administration of a composition that does not include magnesium." (PTX 1.) The patent specification does not use the term "injection site hemolysis" at all, but it does use "hemolysis" often. Most references to "hemolysis" in the specification describe hemolysis rates of rabbit red blood cells when experiments were conducted. (*Id.*) One pertinent mention of "hemolysis" connects the term to intravenous injection of the solution. (*Id.* at 1:61–67.) The specification describes the background of the invention, explaining that tetracyclines (such as minocycline) cause tetracycline-

induced hemolysis, which can "lead to venous phlebitis at the site of injection when administered intravenously, resulting in irritation and potentially limiting the volumes of infusion that can be tolerated." (*Id.*) The specification continues, "It was unexpectedly discovered that the incidence of tetracycline-induced hemolysis can be greatly decreased by formulating the tetracycline with divalent or trivalent cations." (*Id.* 7:31–33.) These references to "hemolysis" in the specification lead the Court to conclude that "injection site hemolysis" is intended to describe hemolysis that results from the intravenous administration of the composition, which can be noticed by a POSA when the injection site shows phlebitis (inflammation), swelling, redness, or other symptoms familiar to a POSA.

The parties appear to be less concerned about the meaning of "injection site hemolysis" and more concerned about the lack of instruction on how to measure its occurrence or reduction. Dr. Klibanov and Dr. Chambers expressed this concern in their testimony. (Tr. 505:6–9, 595:2–597:8.) Plaintiffs respond by citing data in the '802 Patent specification and prosecution history from experimental models that directly measured injection site hemolysis, examined injection site reactions, and examined the effect of the formulation on other cell types. (Dkt. 249 at 8; Tr. 223:11–226:22, 344:13–346:15; PTX-71; PTX-196.) These in vivo[11] and in vitro[12] experiments were conducted in solutions containing minocycline and metal cations, and in

[11] "In vivo" is a scientific term referring to a "laboratory study performed on whole, living organisms, usually animals (including humans) and plants as opposed to a partial or dead organism." *In vivo*, Taber's Medical Dictionary Online (24th ed.).

[12] "In vitro" is a scientific term referring to a "laboratory study performed on isolated tissue, organs, or cells outside their normal context, as proteins in solution, or cells in an artificial culture medium." *In vitro*, Taber's Medical Dictionary Online (24th ed.).

solutions of prior art minocycline (without metal cations) and then compared. (Dkt. 249 at 8.) The experiments showed reduced hemolysis in the solutions containing minocycline and metal cations. (*Id.*) According to Plaintiffs, a POSA would understand this data to show that reduced incidence or risk of injection site hemolysis occurred in a solution containing minocycline and a metal cation. (*Id.*) With this understanding, a POSA would be able to accurately measure the occurrence and reduction of injection site hemolysis in a patient.

Defendant disagrees that the results of these experiments are appropriate benchmarks. They argue that because none of the experiments were performed in live humans, they cannot be used in construing the claim term "injection site hemolysis," a term used in a patent for a drug to be used in live humans. (Dkt. 249 at 11; Tr. 597:18–600:1.) Plaintiffs respond by citing a prior art reference justifying the use of in vitro tests as a valid model for measuring hemolysis in live patients. (Dkt. 249 at 10; Tr. 835:9–23; PTX 177.) *See* D.M. Hoover et al, *Comparison of* in Vitro *and* in Vivo *Models to Assess Venous Irritation of Parenteral Antibiotics*, 14 FUNDAMENTAL & APPLIED TOXICOLOGY 589 (1990).

The Court agrees with Plaintiffs. The '802 Patent specification discusses the signs and symptoms of hemolysis at the injection site, and the experimental data cited in the specification provides a plethora of evidence for a POSA to assess the occurrence and reduction of hemolysis in a patient. Defendant's concern for the applicability of the in vitro experimental models is unpersuasive, because a POSA would be aware that the in vitro experimental models cited in the specification are

reliable and well-known in scientific literature for evaluating injection site hemolysis. (Tr. 123:24–124:3, 124:5–8, 124:24–125:2, 223:11–225:15, 226:23–227:3, 357:4–10.) A POSA would also be aware of the Hoover article cited by Plaintiffs, which was published well before the patents-in-suit were filed and explicitly concludes that in vitro hemolysis tests like the ones Plaintiffs conducted are valid models for measuring hemolysis in humans. *See* Hoover et al., at 597 ("The coordinated use of these in vitro and in vivo models to evaluate venous irritancy may assist preclinical assessment of potential clinical reactions to new parenteral drug formulations."). A POSA therefore would have sufficient information to determine how to measure the occurrence and reduction of hemolysis when using this product.

The understood meanings of "hemolysis" and "injection site," in combination with the '802 Patent specification's references to "hemolysis" and what a POSA would know about measuring the occurrence and reduction of hemolysis leads the Court to adopt the Plaintiffs' proposed definition of "injection site hemolysis." (Dkt. 249 at 7.) Accordingly, this Court construes "injection site hemolysis" to mean "damage to red blood cells that is caused by intravenously administered formulations, which in turn causes a cascade of events that can clinically manifest near the injection site (or downstream therefrom in the blood) in various ways, including, for example, phlebitis, erythema, skin damage / necrosis, thrombophlebitis, and pain."

5. "Subject"

The parties next dispute the claim term "subject." The term "subject" appears once in Claim 1 (and, therefore, in Claims 7 and 18) of the '802 Patent and once in

Claim 1 (and, therefore, in Claim 27) of the '105 Patent: "A method of treating a bacterial infection in a subject . . . ." (PTX-1; PTX-2.) Plaintiffs argue that a "subject" can only be a human, but Defendant argues that "subject" means any animal, including humans. Plaintiffs do not construe this term in post-trial briefings. At trial, however, when Dr. Friedman stated that "subject" means "a human," Defendant objected, and Plaintiffs' counsel explained that he did not think "subject" was a claim construction issue. (Tr. 98:22–99:23.) Plaintiffs' counsel explained that "subject" was defined in the opening report and the patent's specification and was "not something that's new, nor is it claim construction." (Tr. 99:18–23.)

Defendant does address the term "subject" in its post-trial briefings. According to Defendant, "subject" means any animal, including humans. (Dkt. 250 at 18.) Defendant argues that the term cannot be limited to humans because the term "human" is used later in the specification. (*Id.*; *see* PTX-1 at 37:6–15.) Therefore, if the patentee truly meant for "subject" to be limited to humans, the patentee would have used "human" instead of "subject" in this instance. (*Id.*) Accordingly, Defendant argues, "subject" must include all animals in addition to humans.

The Court construes "subject" to match Defendant's construction: "any animal, including humans." The intrinsic evidence cited by Defendant, specifically the '802 Patent and '105 Patent specifications, reveal that the term "subject" should not be limited only to humans. Nowhere in the patent specifications does the patentee express that the composition is to be administered only to human subjects. The term "subject" appears repeatedly throughout the specifications to define the purpose of

the invention (to "treat[] or prevent[] a bacterial infection in a subject") and to explain how the invention could be administered (either "to the subject via a topical route" or "to the subject via an intravenous route"). (PTX-1 at 6:26–51, 19:15–35, 40:43–47; PTX-2 at 6:19–43, 19:3–25, 41:33–36.) Nothing in that language suggests that "subject" is to be limited to humans. The patent specifications do not provide any additional context implying that "subject" is to refer only to humans. On the contrary, the specifications imply the opposite, since all experiments cited in the specifications were conducted on non-humans (specifically, rabbit and sheep red blood cells). (PTX-1; PTX-2). A POSA reading the claim term in the context of the specifications would not, therefore, have any reason to think that "subject" was limited to "humans." Accordingly, this Court holds that "subject" is construed to mean "any animal, including humans."

6. "Does not include magnesium"

The final claim construction dispute is the claim term "does not include magnesium." This term appears once in Claim 1 (and, therefore, in Claims 7 and 18) of the '802 Patent: "A method of treating a bacterial infection in a subject, . . . whereby injection site hemolysis of red blood cells is reduced relative to intravenous administration of a composition that does not include magnesium." (PTX-1.)

Defendant construes the claim term in its post-trial briefing, arguing that the claim term should be construed to mean exactly what it says: "does not include magnesium." (Dkt. 250 at 18–19; Dkt. 254 at 10–11.) Defendant then alleges that Plaintiffs are misconstruing the term to mean "does not include magnesium *or*

another metal cation." (*Id.*) Defendant explains that if the patentee wanted to include other metal cations in this claim term, it would have done exactly that. (*Id.* at 10.) But because the patentee only used the word "magnesium," the claim term must be limited to only magnesium. (*Id.*)

In Plaintiffs' post-trial briefing, they respond that "does not include magnesium" refers to a comparison between the composition and prior art minocycline formulations without metal cations. (Dkt. 251 at 7.) Plaintiffs further argue that all experiments cited in the intrinsic evidence also compare minocycline formulations with metal cations (such as magnesium) to minocycline formulations without metal cations. (*Id.*) Presumably, then, Plaintiffs are arguing for a broadened construction of the claim term—apparently arguing that "does not include magnesium" actually means "does not include any metal cation."

The construction of this claim term was also mentioned briefly at trial. Defendant objected on claim construction grounds to a question asked to Dr. Friedman regarding this claim term, and Dr. Friedman's answer appeared to equate "magnesium" to "metal cations." (Tr. 122:20–123:15.) On cross-examination, when Defendant pressed the issue, Dr. Friedman would not say whether the term "magnesium" necessarily excluded all other metal cations, but he did confirm that magnesium is the particular metal cation that the inventors chose to include in their invention, "the only metal cation that's in the solution," and the only metal cation in Defendant's product. (Tr. 146:17–154:5.)

The Court agrees with Defendant's construction. In some cases of claim construction, the "ordinary meaning of claim language . . . may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words." *Philips*, 415 F.3d at 1314. Such is the case here. The plain and ordinary meaning of "does not include magnesium" describes a formulation that does not include magnesium. The exclusion of any other metal cations is not expressed in any way in the claim language. Plaintiffs used the term "metal cation" in numerous places throughout the patent specification yet chose to limit the claim term to "magnesium." And Plaintiffs' own expert witness confirmed that magnesium is the metal cation specifically chosen to be used in the invention, the only metal cation in the solution. The Court cannot agree with Plaintiffs' interpretation that "does not include magnesium" should be construed to exclude magnesium *and* any other metal cation. Accordingly, "does not include magnesium" is construed to mean "does not include magnesium."

IV. CONTINUED FINDINGS OF FACT: EVIDENCE PRESENTED AT TRIAL

A. The Testifying Witnesses

Five witnesses testified over the course of the trial. As for the credibility of each testifying witness, the Court did not find any witness to lack credibility. Each witness provided believable testimony and did not express any hallmarks of hiding facts or twisting the truth. Instead, any differing testimony about a variety of issues was due to a difference in opinions, which were likely sincerely held by each witness. The Court finds no reason to question the testimony of each witness. What follows in

this Section is an introduction to each testifying witness, and the following Sections describe the expert witnesses' testimony on infringement and invalidity of the Asserted Claims.

1. Dr. Bruce Friedman

Plaintiffs' expert witness Dr. Bruce Friedman testified as an expert in infectious disease complications in critically ill patients, including in the clinical knowledge, use, and administration of tetracycline antibiotics, and in particular the clinical knowledge, use, and administration of intravenous minocycline to patients with infectious diseases. (Tr. 85:22–86:3.)

Dr. Friedman is a medical doctor, professor of internal medicine and anesthesiology, and clinical researcher. He has been practicing for forty years and currently works at a burn and wound hospital. (Tr. 72:15–25.) Dr. Friedman's field of expertise is intensive care medicine with a specialty in burn and wounds, which includes significant work with infectious diseases. (Tr. 84:9–18.)

Dr. Friedman testified that he regularly treats patients with skin injuries, which are often injuries that lead to infectious disease complications. (Tr. 73:6–19.) To treat these patients, Dr. Friedman regularly administers intravenous minocycline to them, which he testified was a very effective medication, and he regularly has four to eight patients on minocycline in any given week. (Tr. 74:1–6.) He has treated approximately one thousand patients with the prior art minocycline. (Tr. 76:13–15.) He has treated approximately ten thousand patients with Minocin and no longer treats patients with the prior art minocycline. (Tr. 78:17–21.) When asked about his

familiarity with intravenous minocycline products on the market, Dr. Friedman testified that he was aware of two: the prior art minocycline, and Minocin. (Tr. 74:7–10.) He stated that he understood that the two were different because Minocin included the addition of magnesium cations. (Tr. 74:11–16.) He testified that Minocin improved the prior art minocycline because it adjusted the pH to be slightly higher, which, in combination with adding magnesium cations, enabled the product to be delivered to the patient at a lower volume. (Tr. 78:2–7.) Dr. Friedman testified that these changes made Minocin a more tolerable and reliable product than the prior art minocycline. (Tr. 78:8–11.)

2. Dr. Tina deVries

Plaintiffs' expert witness Dr. Tina deVries testified as an expert witness regarding all aspects of pharmaceutical research and development, drug formulation, the FDA regulatory approval process for drug products, and the FDA process for making changes to drug product labels, and specifically regarding aqueous pharmaceutical compositions of tetracyclines, including minocycline and doxycycline, in combination with metal cations in preparation as a pharmacist of intravenous formulations. (Tr. 202:6–14.)

Dr. deVries is a pharmaceutical development scientist with over thirty years of experience in pharmaceutical research and development, along with experience in "all aspects of FDA requirements and the drug product approval process" for both generic and patented drugs. (Tr. 192:25–193:6, 196:15–18; PTX-129.) As part of that FDA experience, Dr. deVries has personally and directly communicated with the FDA

regarding drug product labels and approvals. (Tr. 198:21–199:2.) She has specific experience in formulation development, which involves determining how to transform a powder drug into an aqueous product suitable for intravenous administration to patients after combining it with other ingredients. (Tr. 195:12–25.) Dr. deVries has never worked on an intravenous formulation of a tetracycline (such as Minocin), but she maintained that her experience is directly relevant to her testimony in this case because she has worked on products before they are dissolved into a solution suitable for intravenous administration. (Tr. 199:19–200:8.) She has also supervised and observed several projects involving minocycline and a divalent metal cation, including magnesium. (Tr. 200:9–14.)

3. Mr. David Griffith

David Griffith, a nonparty witness, is one of the inventors listed on the patents-in-suit. (Tr. 317:1–3.)

Griffith began initial research on Minocin in 2005 while working as the director of nonclinical and clinical sciences at Mpex Pharmaceuticals. (Tr. 318:5–7.) He does not have experience administering tetracyclines, although he does have experience diluting them. (Tr. 381:19–382:3.) He clarified that his research on Minocin was his first interaction with tetracyclines, and he became familiar with the properties of tetracyclines by reading literature. (Tr. 386:2–9.) That research led him to understand that tetracyclines had issues with storage, stability, tolerability, and low pH. (Tr. 391:19–392:14.) Around 2011, Mpex became Rempex Pharmaceuticals, and

Griffith, along with the other inventors, acquired the NDA for Minocin. (Tr. 318:8–13.)

Griffith testified that the '105 Patent and the '802 Patent related to a new formulation of the antibiotic minocycline that sought to improve the low pH, which led to injection site pain and inflammation, and large infusion volumes required by the prior art minocycline. (Tr. 320:7–14, 323:15–324:7.) Griffith stated that he understood that the prior art minocycline had a low pH (between 2.0 and 2.8 for the reconstituted solution) in order to make it more stable. (*Id.* 325:7–20, 326:12–17.) He explained that in order to increase the pH of the prior art minocycline to make it suitable for administration, the solution needed to be diluted in large volumes of diluent in order to avoid venous tolerance issues. (Tr. 328:8–18.) After dilution, the pH would rise to 2.5 to 4, which Griffith testified was still quite low. (Tr. 328:25–329:5.) Griffith testified that administering a solution with such a low pH caused injection site pain, a side effect described on the prior art minocycline's product label. (Tr. 329:6–13.) In addition to the low pH causing injection site problems, the large injection volume was a problem with the prior art minocycline. Griffith explained that the product needed to be administered to patients twice a day every day for ten to fourteen days, which was a very a high volume of intravenous fluid to enter a body and could have a harmful effect on patients who needed other drugs. (Tr. 331:2–18.)

Griffith began working with dimethylamino tetracyclines such as minocycline because it was effective against a particular type of bacteria (Acinetobacter baumannii). (Tr. 322:17–323:14.) Griffith and the other inventors began

experimenting with molar ratios of 3:1 (magnesium:minocycline), which caused solubility and stability issues. (Tr. 332:1–9.) They changed their approach and began using a 10:1 molar ratio of magnesium to minocycline, which they found to "surprisingly" lead to more stability. (Tr. 332:13–17.) Along with an increased molar ratio, Griffith and the other inventors unexpectedly found that they could change pH of the formulation and still maintain stability. (Tr. 333:14–16.) In addition, they unexpectedly found that the formulation blocked hemolysis. (Tr. 333:17–334:3.) Because of the higher pH and reduced hemolysis in the newer formulation, the inventors realized that the formulation could be diluted into a lower volume of solution to prepare it for administration. (Tr. 334:4–11.) Griffith testified that each of these benefits is described in the '802 Patent specification. (Tr. 335:6–21.)

Griffith explained that the specification also lists examples of several tests that the inventors performed, which varied different properties of the Minocin formulation to compare it to the prior art minocycline (Tr. 336:15–19.) One experiment they performed used the same formulation but with doxycycline, a different tetracycline, instead of minocycline, but they found that the same formulation using doxycycline caused solubility issues—the same issues they had expected with minocycline. (Tr. 343:10–344:11.) They performed several in vitro experiments to test hemolysis reduction in the formulation. (Tr. 344:21–351:6.) They discovered that their new formulation, which added divalent cations (such as magnesium) to minocycline at a higher molar ratio resulted in "significant inhibition" of hemolysis and "improve[d]

venous tolerance" compared to the prior art minocycline that did not include divalent cations. (Tr. 350:24–351:10, 360:21–361:6.)

Griffith testified that from 2011 to 2015, he was involved in discussions with the FDA regarding the process of getting FDA approval for the new minocycline formulation. (Tr. 364:22–365:24.) They initially sought a 505(b)(2) mechanism, which would have used previous findings of efficacy and safety of a previously approved minocycline product, but the approach changed when they decided to acquire that product directly. (Tr. 366:3–23.) They filed a supplemental NDA for their new minocycline product, and the previous formulation was removed from the market. (Tr. 367:1–368:4.) The new formulation included an updated label noting the changes in pH level and volume of fluid for administration. (Tr. 368:5–11.) There were some discussions with the FDA about potential human clinical studies for the new formulation, but those studies were not performed because they were not required for approval of the new formulation. (Tr. 372:16–373:12.) He clarified on cross-examination that the FDA would have required clinical trials if Plaintiffs wanted to remove standard information about tetracyclines (such as risk of hemolysis) to show how the new formulation differed from the original formulation, which they decided not to do. (Tr. 382:8–18.) Instead, the FDA's approval relied on data from the experiments and tests Griffith conducted. (Tr. 373:13–18; *see* PTX-71.) Without the clinical trial, the FDA therefore approved a label including the improved pH and lower infusion volume but without a claim of improved tolerability or reduced injection site hemolysis. (Tr. 384:7–385:25.) The FDA approved the new minocycline

formulation with magnesium at a 5:1 molar ratio to minocycline with a reduced infusion volume of 100 mL to 1,000 mL and a higher pH. (Tr. 380:7–17.)

On cross-examination, Defendant's counsel questioned Griffith about the literature he read before creating the Minocin formulation. Griffith first testified that the patents-in-suit describe the use of a 7-dimethylamino-tetracycline (such as tetracycline, glycylcycline, doxycycline, and minocycline) with a metal cation (such as magnesium, calcium, or iron), but the patents-in-suit specifically focus on minocycline with magnesium. (Tr. 421:9–19, 422:1–10.) Defendant asked Griffith about a 2006 patent that lists minocycline as an active component and identifies magnesium as a preferable metal for complexing. (Tr. 424:13–426:4; DTX-11.) Griffith stated that even though this patent discussed using divalent cations with tetracyclines, the patent used a much lower molar ratio, and Griffith's higher molar ratios had not been tested before. (Tr. 426:8–18.) Griffith explained that it was commonly known information that there were issues with combining metal cations with tetracyclines, and no one had ever tested that formulation as a higher concentration because the assumption was that the formulation would be insoluble and create no new benefits. (Tr. 426:8–24.)

4. Dr. Alexander Klibanov

Dr. Alexander Klibanov, Defendant's expert witness, testified as an expert in medicinal chemistry and pharmaceutical formulations. (Tr. 462:12–13.) Dr. Klibanov is a professor of chemistry and bioengineering with expertise in pharmaceutical formulation and medicinal chemistry. (Tr. 459:18–460:3.) Dr. Klibanov has published

hundreds of publications and owns over thirty patents. (Tr. 460:12–21.) He is a consultant for several pharmaceutical companies, member of numerous journal editorial boards, and has received many professional awards for his work. (Tr. 461:1–22.) Dr. Klibanov testified that he has substantial experience in tetracycline formulation, and he has been involved in many projects involving intravenous formulations. (Tr. 464:6–15.) Dr. Klibanov has not, however, treated a patient with minocycline. (Tr. 528:24–529:1.) Nor, according to his testimony, has he been involved in any FDA tetracycline drug approval process. (Tr. 530:5–9.)

5. Dr. Henry Chambers

Defendant's expert witness Dr. Henry Chambers testified as an expert in the field of treatment of infectious diseases and the use of antimicrobial agents, including tetracyclines and minocycline. (Tr. 570:19–579:22.) Dr. Chambers is a physician specializing in infectious diseases. (Tr. 565:9–15.) He has published hundreds of publications in the field of infectious diseases and serves as editor on the Stanford Guide, a manual covering bacterial infections and other infectious diseases. (Tr. 567:1–24.) This manual includes information on minocycline, but Dr. Chambers has never personally prescribed or used intravenous minocycline. (Tr. 568:5–10, 568:25–569:10, 571:12–572:11.)

Dr. Chambers has never had occasion to use intravenous minocycline because it is "almost identical in terms of spectrum" to doxycycline, which is his go-to tetracycline antibiotic. (Tr. 569:3–10.) He explained that doxycycline and minocycline have minor differences on the top of their chemical structure, but are identical on the

bottom of the structure, which is where the antibacterial interaction happens. (Tr. 683:4–14.) When probed about this testimony on cross-examination, he conceded that minocycline and doxycycline do have some differences. Dr. Chambers testified that minocycline is more active than doxycycline against Acinetobacter baumannii, the bacteria Minocin treats, as well as other bacteria. (Tr. 630:3–631:23.) He added on cross-examination that he did not have any firsthand experience with whether intravenous minocycline formulations have any injection site tolerability issues such as phlebitis, thrombophlebitis, erythema, pain, or skin necrosis. (Tr. 632:11–633:12.) Nor does he have any firsthand experience reconstituting minocycline or selecting a diluent in order to prepare the formulation for administration to patients. (Tr. 633:13–20.) Dr. Chambers does have experience preparing intravenous formulations for administration to patients, a process that is driven by the instructions on the product label. (Tr. 570:5–18.)

Dr. Chambers has participated in clinical trials involving the use of minocycline, including one with Minocin. (Tr. 573:13–15, 573:16–574:9; PTX-139; PTX-140.) When asked about this clinical trial on cross-examination, Dr. Chambers agreed that minocycline is one of very few antimicrobials that is effective against Acinetobacter baumannii and other multidrug-resistant bacteria. (Tr. 637:5–10, 640:17–641:20.) He also agreed that one of the benefits of the Minocin formulation, which was always diluted with 100 mL of normal saline before administering to a test patient, is a lower minimum injection volume of 100 mL. (Tr. 638:1–639:20.)

D. Rounds One and Two: Testimony on Infringement

The bench trial proceeded in four rounds of testimony. Round One consisted of Plaintiffs' evidence on infringement. Round Two consisted of Defendant's testimony on non-infringement and invalidity (obviousness and Section 112 arguments). Round Three consisted of Plaintiffs' response on invalidity and offering secondary considerations. Round Four consisted of Defendant's response to the secondary considerations. This Section discusses both parties' testimony on infringement, which was presented in Rounds One and Two.

1. Dr. Bruce Friedman's Testimony on Infringement

On the issue of infringement, Dr. Friedman concluded, based on his knowledge, experience, and review of the available literature, that "there was induced and contributed-to infringement by [Defendant]." (Tr. 87:16–23.) His conclusion was based on a three-part methodology: (1) determining what elements are required by the asserted patent claims, including the plain and ordinary meaning and a POSA's understanding; (2) determining whether physicians would directly infringe on the claims when using the ANDA product; and (3) determining whether Defendant intends to and will encourage, recommend, or promote a physician to perform the claimed methods, including whether the ANDA product has no other substantial non-infringing use. (Tr. 91:18–92:6.)

When he analyzed whether Defendant indirectly infringed on the patents-in-suit, Dr. Friedman focused on the ANDA product label and how a POSA might interpret that label when administering the product and compared it to Minocin and

the prior art minocycline. (Tr. 93:1–6.) He testified about the ANDA's common technical document summaries (PTX-021), a document which was provided to the FDA as part of Defendant's ANDA filings. (Tr. 94:10–16.) He testified that the ANDA product and Minocin were identical to each other and used the same ingredients: same amount of minocycline, same amount of magnesium, and an adjustment of the pH. (Tr. 94:22–95:3.) The ANDA product would therefore have the same benefits of Minocin (reduced delivery volume, stabilized pH, reduced tolerability issues). (Tr. 96:3–13.)

a. Claim 1 of the '802 Patent

Dr. Friedman testified about each of the claims at issue. He concluded that a physician following the ANDA label would infringe on Claim 1 of the '802 Patent because the label instructs that it is meant to treat bacterial infections (like Minocin) and explains how to reconstitute and administer the ANDA product. (Tr. 101:9–17.) A POSA would understand that the "composition" discussed in Claim 1 meant the reconstituted solution (which he noted to be different than the diluted solution) because the '802 Patent specification repeatedly defines the "composition" as such. (Tr. 101:18–103:22.) A POSA would mix that "composition" with a diluent as specified in the label, and then it would be ready for intravenous administration. (Tr. 104:1–5.) A POSA administering the ANDA product would go through that same process. (Tr. 6–10.)

Dr. Friedman also testified that a POSA would understand that the reconstituted solution mentioned in Claim 1 of the '802 Patent meant a solution

consisting of minocycline, magnesium, a base, and a water-based solvent. (Tr. 106:21–25.) He testified that the ANDA product infringed on this Claim 1 because its label specified the same ingredients: minocycline, magnesium, a base (sodium hydroxide), and a solvent (sterile water). (Tr. 107:2–9.) A physician following the ANDA label would, therefore, meet this element of Claim 1. (Tr. 12–14.)

Dr. Friedman testified that a POSA following the ANDA label would also meet the molar ratio element of Claim 1. Claim 1 states that the molar ratio of magnesium to minocycline is greater than about 4:1. (PTX-001.) Dr. Friedman testified that the ANDA product meets that element because it defines the amount of minocycline and the amount of magnesium in the product, and when a POSA calculates those amounts in terms of molar ratio, it is about a 5:1 ratio, which meets the "greater than about 4:1" element. (Tr. 108:3–11.)

He then testified that a POSA following the ANDA label would meet the pH element of Claim 1. That element states that the composition has a pH "that is no less than 4 and no greater than 6." (PTX-001.) The ANDA product label would meet that claim element because it states that the pH for the product is between 4.5 and 5. (Tr. 109:1–4.)

Dr. Friedman testified that the ANDA would also meet the injection site hemolysis element of Claim 1. A POSA would understand what injection site hemolysis meant and would understand the benefits of a product that reduced hemolysis. (Tr. 114:4–116:9.) He testified about several properties of a product that affects the rate of hemolysis. First, an "unexpected discovery" revealed that hemolysis

could be decreased by formulating minocycline with a divalent cation with high molar ratios. (Tr. 116:12–16.) He also explained that a pH level that is too low (around 2 to 4) would trigger injection site hemolysis. (Tr. 117:5–24.) A higher injection volume triggers higher hemolysis as well, a fact he testified would be commonly known based on several publications coming to that conclusion. (Tr. 117:25–118:8, 119:18–12012; PTX-231; PTX-188; PTX-225.) The Minocin product helped resolve the issue of injection site hemolysis because Minocin's high molar ratio allowed the pH to be adjusted to a physiologic range, which in turn permitted the reduction of the volume of delivery. (Tr. 121:18–23.) Due to these changes, injection site hemolysis and tolerability issues were greatly diminished when Minocin was used as compared to a formulation without magnesium. (Tr. 122:1–8.) On cross-examination, Defendant pressed Dr. Friedman about whether each patient who received the prior art minocycline truly experienced observable injection site hemolysis and other tolerability issues. (Tr. 155:24–159:25.) Dr. Friedman conceded that each patient likely experiences different symptoms of hemolysis, but he maintained an opinion that the tolerability issues with the prior art minocycline were "well-known in the literature." (Tr. 156:13–158:16.)

Dr. Friedman testified that a POSA would know that reduced injection site hemolysis would be a benefit of Minocin simply by looking at the formulation and ingredients. (Tr. 123:20–23.) The ANDA product label discloses a similar reduction of injection site hemolysis because it specifies a higher pH range, a reduction in injection volume, and the inclusion of magnesium. (Tr. 125:3–126:8.) A POSA following the

ANDA label would, therefore, meet the injection site hemolysis element of Claim 1, according to Dr. Friedman. (Tr. 126:9–11.)

On cross-examination on the hemolysis issue, Defendant questioned Dr. Friedman about the lack of clinical trials on hemolysis. Defendant cited a letter from the FDA when Minocin was in the approval process, in which the FDA discussed running clinical trials to support the statement on Minocin's label that the product would reduce hemolysis and tolerability issues as compared to the prior art minocycline. (Tr. 163:9–23; DTX-131.) This discussion was not a recommendation to perform a trial and cited later communications where the FDA stated that a trial was not necessary. (Tr. 163:24–164:11.)

b. Claims 7 and 18 of the '802 Patent

Dr. Friedman next testified that the ANDA product meets Claims 7 and 18 of the '802 Patent, both of which depend from Claim 1. Claim 7 states that the composition has a pH "between about 4.5 to about 5.5," and the ANDA label specifies that its solution has a pH of 4.5 to 5. (Tr. 126:18–127:10.) Claim 18 states that the total volume of the composition administered is less than 500 mL, which a POSA would understand to mean the diluted solution prepared for administration to a patient. (Tr. 127:22–128:14.) And the ANDA product label states that the product can be administered from 100 to 1000 mLs, but Dr. Friedman testified that this meets Claim 18 because a POSA would always choose to administer the minimum permissible volume. (Tr. 129:9–21.) Accordingly, Dr. Friedman concluded that a physician following the ANDA label would meet Claims 7 and 18 of the '802 Patent.

c. Claims 1 and 27 of the '105 Patent

Claim 27 of the '105 Patent depends from Claim 1, which Dr. Friedman testified to be substantially similar to Claim 1 of the '802 Patent. (Tr. 132:3–13.) Dr. Friedman's conclusions relating to the ingredients (minocycline and magnesium), injection volume, pH level (between 4 and 7), and molar ratio (greater than 3:1) in the '802 Patent apply equally to the '105 Patent. Thus, a physician following the ANDA label would meet those claim elements of Claim 1. (Tr. 132:22–135:17.)

The '105 Patent also includes an element on osmolality, which Dr. Friedman defined as a measure of the weight of particles in a solvent in milliosmols per kilogram, a measurement that can be easily calculated and is often calculated by the pharmacy. (Tr. 135:22–136:3, 138:7–10.) Claim 1 of the '105 Patent defines an osmolality of "less than about 500 mOsmol/kg." (PTX-002.) The general physiologic standard of care, which is supported by several publications, is to maintain osmolality of less than 500 mOsmol/kg. (Tr. 136:15–137:9; PTX-184; PTX-229.) Dr. Friedman testified that the ANDA product infringes this osmolality element of Claim 1 because the ANDA also inevitably will have an osmolality less than 500 mOsmol/kg to be within the standard of care. (Tr. 140:2–21, 430:8–18.) Even though the ANDA label doesn't expressly mention osmolality, it is still infringing because osmolality can be easily calculated by looking at the ingredients listed on the label. (Tr. 141:10–142:4.) A pharmacist, who typically mixes the drug, is often the one who calculates the osmolality of a formulation before sending it to the patient, but osmolality is nevertheless not a complex calculation. (Tr. 435:7–19.) He concluded that a physician

following the ANDA label would therefore meet the osmolality element of Claim 27. (Tr. 143:23–25.)

2. Dr. Tina deVries's Testimony on Infringement

(a) Claims 1, 7, and 18 of the '802 Patent

Dr. deVries testified about the FDA regulatory process for Minocin and any generic drug that copied Minocin. Because Minocin is parenterally (intravenously) administered, it must be a solution to be suitable for administration, and FDA regulations require a copy of an aqueous parenteral drug to have the same active and inactive ingredients in the same amounts as the patented drug. (Tr. 205:24–206:5.) This means, by necessity, that the ANDA product is required to exactly copy Minocin. (Tr. 206:19–21.) Because the copy of the drug is the same as the original, clinical trials are not necessary. (Tr. 206:15–22, 254:5–12.) Dr. deVries testified that these regulatory requirements, in combination with Defendant's literature search when creating the ANDA product, showed that Defendant knew its product would infringe on Plaintiffs' patents. (Tr. 208:20–211:14.)

Dr. deVries compared the Asserted Claims to the ANDA product and label when analyzing whether the ANDA product infringed. Minocin and the ANDA product share the same properties: (1) treat only bacterial infections; (2) administered only intravenously, (3) described as minocycline for injection, (4) ingredients include minocycline, magnesium, and a base; (5) the same amounts of each of those ingredients; (6) a molar ratio of greater than 4:1; and (6) a pH of the reconstituted solution between 4 and 6. (Tr. 212:15–218:15.) The pH stated in Claim

7 of the '802 Patent (between about 4.5 to about 5.5) refers to the pH of the reconstituted solution, not the diluted solution, and Dr. deVries cited a reference to support that opinion. (Tr. 218:11–221:25; 271:11–21; PTX-225.)

Defendant cross-examined Dr. deVries on the volume element of Claim 18. Defendant noted that the Minocin label permits the reconstituted solution to be diluted in up to 1,000 mL of diluent, whereas Claim 18 limits the total volume of the administered composition to be less than 500 mL. (Tr. 274:7–10; PTX-130.) Dr. deVries testified that a physician who administers anywhere between 501 and 1,000 mL as permitted by the label would not meet the elements of Claim 1. (Tr. 274:16–275:7.) But she stressed that no physician would choose to administer that high of a volume to a patient because it would be against the standard of care; rather, any physician would choose to administer the lowest volume permitted by the label, which is 100 mL. (Tr. 274:11–23.) Dr. deVries testified that the ANDA label also specified an administration volume ranging from 100 mL to 1,000 mL, and a physician following this label would also choose to administer the lowest volume possible. (Tr. 275:16–25.)

Dr. deVries then discussed the various studies and experiments on hemolysis that Plaintiffs conducted and submitted to the FDA during the approval process for Minocin. (Tr. 223:11–225:5; PTX-71; PTX-196.) Plaintiffs did not conduct any clinical trials in patients relating to Minocin's improved tolerability claim. (Tr. 252:4–5.) This is because the FDA did not require additional human clinical trials on the hemolysis claim, as the label clearly states the improved pH and improved injection volume. (Tr.

251:3–10.) Clinical trials would have been necessary had Plaintiffs sought to make a change to the clinical claim, something Dr. deVries called "class labeling" that would have the effect of changing the clinical claim for all formulations of all tetracyclines. (Tr. 251:11–19.)

Dr. deVries testified that the inventors conducted some experiments on animals such as mice (because human trials would be harmful), which were still applicable because the experiments studied the same type of blood cells in animals that also appear in humans and would cause the same type of injection site hemolysis. (Tr. 225:6–13.) These studies varied the molar ratio, pH, and other properties and compared the results to a formulation without magnesium to discover whether the formulation with magnesium reduced injection site hemolysis. (Tr. 225:20–226:15.) What they found is that a higher pH and an "unexpected" discovery of a high ratio of magnesium to minocycline were associated with lower injection site hemolysis. (Tr. 284:18–285:5.) Dr. deVries testified that these experiments are well-recognized and reliable models for evaluating injection site hemolysis. (Tr. 227:2–3.) The FDA granted approval to Minocin to completely replace the prior art minocycline because the experiments showed that Minocin reduced the risk of injection site hemolysis as compared to a formulation without magnesium. (Tr. 227:23–228:6.)

Dr. deVries testified that when Defendant submitted its ANDA to the FDA, it explained that its product included magnesium, and that the function of magnesium was hemolysis reduction. (Tr. 230:9–19.) Defendant repeatedly stated that the purpose of magnesium in its ANDA product was to reduce injection site hemolysis.

(Tr. 230:23–231:22; PTX-22; PTX-206; PTX-207; PTX-210; PTX-211.) The FDA then confirmed to Defendant that magnesium in its product was used for hemolysis reduction. (Tr. 231:23–232:8; PTX-220; PTX-19.) Dr. deVries testified that based on this evidence, use of the ANDA product according to its label would meet the elements of Claims 1, 7, and 18 of the '802 Patent. (Tr. 232:16–233:8.)

On cross-examination, Dr. deVries conceded that the ANDA product label does not explicitly state that the product will reduce injection site hemolysis. (Tr. 247:4–14.) But just looking at the information on the label would inform her and any other POSA that hemolysis will be reduced and there will be better tolerability as compared to the prior art minocycline. (*Id.*)

(b) Claims 1 and 27 of the '105 Patent

Dr. deVries's conclusions about the '802 Patent applied equally to the same claim elements and limitations that appear in Claims 1 and 27 of the '105 Patent. (Tr. 233:9–14.)

She then went into the osmolality element of Claim 1, which states an "osmolality less than about 500 mOsmol/kg." (PTX-002.) Dr. deVries defined osmolality as a property related to the concentration of dissolved molecules or particles in a solution such as an intravenously administered drug. (Tr. 234:1–13.) Osmolality is not mentioned on either Minocin's label or the ANDA product's label, but it is not necessary because osmolality can be calculated based on the amounts of ingredients in the composition that are listed on a product's label. (Tr. 235:22–236:6; 252:14–20.) The osmolality stated in the specification describes the osmolality of the

reconstituted solution, not the admixture, because Claim 1 is describing the reconstituted solution and not the admixture. (Tr. 237:17–239:1.) Accordingly, the osmolality of less than 500 mOsmol/kg listed in the specification is based on the amounts of three ingredients in the composition: magnesium, sodium hydroxide, and 5 mL of water. (Tr. 238:16–25.) When the reconstituted solution is diluted to prepare it for administration to a patient, it should be isotonic, meaning having the same osmolality as blood (around 300 mOsmol/kg). (Tr. 241:3–14, 261:20–21.)

On cross-examination, Dr. deVries was questioned about a manufacturing process development report that Plaintiffs had sent to the FDA when developing Minocin. (DTX-75.) Defendant noted that this report noted the use of 10 mL for reconstitution of the solution in osmolality tests. (Tr. 265:16–21.) Dr. deVries clarified that she understood that a 10 mL vial was used in these tests, rather than 10 mL used in the solution. (*Id.*) She testified that if the results of this experiment were calculated for 5 mL for reconstitution, she approximated that the osmolality would double. (Tr. 307:20–308:5.)

Dr. deVries testified that this same composition was used in the ANDA product and specified on its label, which would necessarily mean that administering the ANDA product according to its label would also result in an osmolality of less than 500 mOsmol/kg. (Tr. 240:14–20.) Dr. deVries testified that in her opinion, the label for the ANDA product would encourage, recommend, and promote physicians to administer the ANDA product intravenously, an act that would meet every Asserted

Claim. (Tr. 244:12–245:6.) Accordingly, she concluded, there will be direct infringement, and Defendant induced that infringement. (Tr. 244:24–245:6.)

3. Dr. Alexander Klibanov's Testimony on Infringement

Dr. Klibanov testified of his opinion that Defendant did not infringe on Plaintiffs' product. His opinion is largely based on a disagreement with the meaning of the terms "composition" and "administer" in the patents-in-suit specifications. Dr. Klibanov understands "composition" to be limited to the three listed components (minocycline, magnesium, and a base), so the Minocin label instructing a physician to "administer" the "composition" would mean administering those three ingredients (the reconstituted solution) without a diluent. (Tr. 521:20–522:20.) He testified that the ANDA label, on the other hand, instructs the administration of a diluted solution, not the reconstituted solution. (Tr. 522:25–523:3; DTX-0101.) Dr. Klibanov's opinion is that a POSA administering the ANDA product could not infringe on the claim elements of the '802 Patent because the POSA would follow the instructions on the ANDA product label requiring him to add a diluent—which he testified was not a component of the '802 Patent. (Tr. 524:16–525:10.) Accordingly, Dr. Klibanov testified, there can be no infringement. (Tr. 525:10.)

On cross-examination, Dr. Klibanov testified that he understood there are no differences between the ANDA product and Minocin. (Tr. 549:21–23.) Although he would not concede that Defendant copied Minocin with its ANDA product, Dr. Klibanov did agree that all ingredients and amounts of ingredients between the two

products in their reconstituted forms are identical as required by law. (Tr. 549:24–551:5.)

4. Dr. Henry Chambers's Testimony on Infringement

Dr. Chambers testified that there are three primary differences between the ANDA product label and the Minocin label: (1) description of what is in the vial; (2) how the drug is diluted; and (3) warnings relating to potential side effects of magnesium. (Tr. 581:12–20; DTX-101; DTX-110.) He also compared the old and new Minocin labels, testifying that they are essentially the same except for different volume administration, pH, and diluent volume. (Tr. 583:9–20.) Dr. Chambers's understanding about the pH level on the label is that it describes the pH of the solution after dilution, because the diluted solution is what is actually administered to the patient. (Tr. 584:2–9.) On cross-examination, he agreed that the Minocin product has an overall improved pH profile compared to the prior art minocycline, which is beneficial because the higher pH profile in Minocin means a lower likelihood of irritation, pain, and toxicity issues. (Tr. 643:17–644:24.) He also testified that there is no relationship between pH levels, volume of administration, and injection site hemolysis, because that relationship is not demonstrated on the label. (Tr. 584:18–22.)

(a) <u>The '105 Patent</u>

Dr. Chambers testified that the ANDA label does not provide any instructions on osmolality, but a physician would likely ensure that the product is administered at an osmolality "around 500," a measurement that can be easily calculated by

knowing the osmolality of the other ingredients in the product. (Tr. 585:14–586:21, 634:4–25.) Accordingly, Dr. Chambers's opinion was that the ANDA label does not infringe because it does not include any information about osmolality on the label, which means it cannot encourage a physician to aim for a particular osmolality. (Tr. 588:2–14.)

(b) The '802 Patent

For the same reason, Dr. Chambers testified that Defendant did not induce infringement on the injection site hemolysis claim in the '802 Patent because hemolysis is not mentioned in the Minocin label. (Tr. 590:8–9.) He testified that the label only mentions hemolytic anemia and thrombophlebitis, neither of which are a direct mention of hemolysis. (Tr. 590:9–592:19.) In his opinion, neither phlebitis nor thrombophlebitis (which are mentioned on the Minocin label) are related to hemolysis. (Tr. 597:9–17.) He added that the in vitro tests cited by Plaintiffs in support of the opposing opinion are not sufficient comparators to measuring injection site hemolysis in a patient because those test conditions are very sensitive, so in vitro test results do not apply equally to how a product might affect a human patient. (Tr. 597:20–599:21.) Dr. Chambers was not aware of any agreed-upon definition of the term "injection site hemolysis," nor any description of its occurrence and how to measure it. (Tr. 596:17–597:8.)

On cross-examination, Dr. Chambers did not recall reviewing statements by Defendant to the FDA that the function of magnesium in its ANDA product was for hemolysis reduction. (Tr. 656:5–20.)

E. Rounds Two, Three, and Four: Testimony on Obviousness

This Section discusses both parties' testimony on the obviousness element of invalidity, which includes both parties' arguments on secondary considerations. This testimony was presented in Rounds Two, Three, and Four.

1. Dr. Alexander Klibanov's Testimony on Obviousness

Dr. Klibanov testified about the basics of intravenous pharmaceutical formulations, including how a solid drug product cannot be administered intravenously but must be dissolved first. (*See* Tr. 465:1–466:16.) He testified that when developing an intravenous formulation, the formulator would consider stability, solubility, and tolerability of the drug. (Tr. 466:17–468:10.)

He explained that pH and osmolality are important to intravenous administration because the pH and osmolality levels of a formulation should be close to the pH and osmolality levels of blood in order to reduce stress on the patient's body. (Tr. 468:24–470:8.) Dr. Klibanov testified as to the chemical structure of tetracyclines, which is a class of drug compounds that treats bacterial infections. (Tr. 470:14–19.) All tetracyclines share a chemical structure, but minocycline differs from other tetracyclines in specifically the upper portion of the molecule. (Tr. 470:20–22; 474:2–7.) All tetracyclines are able to strongly bind magnesium by forming a complex called a chelate. (Tr. 475:7–16.)

Dr. Klibanov testified about the prior art minocycline and its label. The prior art minocycline label taught that the product was used to treat bacterial infections, and it was a solid powder that needed to be reconstituted in water and then further

diluted to a total volume of 500–1,000 mL to make it suitable for administration. (Tr. 478:10–479:3.) Depending on the type of diluent used, the pH of prior art minocycline varied from 2.0 to 2.8 after reconstitution and 2.5 to 6 after dilution. (Tr. 480:10–481:9.) He testified that a POSA would likely not care about the reconstitution pH and would instead focus on the diluted pH because that is what gets administered into the patient's body. (Tr. 481:4–9.) Dr. Klibanov testified that there were no significant problems with the prior art minocycline, but if a POSA wanted to improve the formulation, he would review literature on minocycline. (Tr. 482:22.5–11.) Two such references Dr. Klibanov discussed were a Chinese patent application referred to as CN'268 (2008) and a patent application referred to as Gibbs (1989). (Tr. 482:12–16, 489:8–12; DTX-0014; DTX-0012.)

(a) Prior Art Reference CN'268

CN'268 discusses improving doxycycline (a tetracycline that is similar to minocycline) by adding magnesium ions in order to increase pH values and minimize irritability when administered. (Tr. 483:7–25.) CN'268 achieved better solubility, stability, and tolerability by adding magnesium ions to the formulation. (Tr. 484:1–3.) CN'268 increased solubility in the formulation, which then allowed a lower volume in administration. (Tr. 485:21–24.) CN'268 used magnesium ions in higher molar ratios to doxycycline and had a pH value between 3 and 7. (Tr. 486:1–9.)

Dr. Klibanov testified that CN'268 would be relevant to a researcher seeking to improve prior art minocycline because CN'268 studies doxycycline, a close relative of minocycline with structural similarities. (Tr. 486:19–24.) And even though CN'268

is not an intravenous formulation, it would still be relevant from Dr. Klibanov's perspective because CN'268 is also an injectable formulation that happens to be injected into the muscle as opposed to the vein. (Tr. 487:1–12.) CN'268 is also a product designed for veterinary use, which Dr. Klibanov considered to be irrelevant because animals are well-established models for human drug administration. (Tr. 487:16–488:4.) Dr. Klibanov testified that a POSA looking to modify the prior art minocycline would, upon reviewing CN'268, be motivated to add magnesium to a minocycline intravenous formulation to improve stability, solubility, tolerability, and pH. (Tr. 489:1–7.) On cross-examination, Dr. Klibanov confirmed that CN'268 does not mention minocycline, and that he did not discuss on direct examination the function or effects of other ingredients (also called excipients) included in the CN'268 formulation. (Tr. 540:19–541:20.)

(b) Prior Art Reference Gibbs

Dr. Klibanov also testified about a second publication, referred to as the "Gibbs" reference. (DTX-0012.) Gibbs researched adding magnesium ions to minocycline at a molar ratio between 1:1 and 8:1, a formulation that resulted in "improved formulation properties." (Tr. 489:8–490:14.) The Gibbs formulation used the same ingredients as the prior art minocycline but added magnesium, because magnesium formed chelates with doxycycline and minocycline, causing beneficial effects (such as improved solubility and stability and reduced toxicity and irritability). (Tr. 491:16–492:13, 500:14–23.) Dr. Klibanov explained that doxycycline and minocycline were listed together in the Gibbs reference more than two dozen

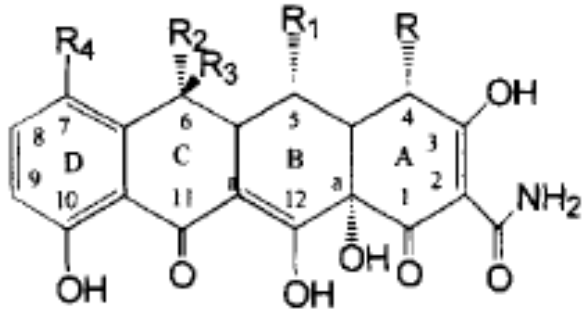
times, which a POSA would understand to mean that doxycycline and minocycline are essentially interchangeable in terms of their interaction with magnesium. (Tr. 491:21–492:4.) When read in relation to CN'268, Dr. Klibanov testified that Gibbs reinforced the idea that what CN'268 revealed about doxycycline's relationship with magnesium also applies to minocycline. (Tr. 492:5–13.) But on cross-examination, Dr. Klibanov conceded that Gibbs does not expressly disclose any data on minocycline formulations but instead focuses on doxycycline formulations. (Tr. 541:25–542:12.) Dr. Klibanov maintained, however, that the doxycycline examples specified in Gibbs provide procedures for making minocycline formulations, and a POSA could follow the procedure specified for doxycycline but use minocycline instead. (Tr. 544:22–547:2.)

(c) Additional Prior Art References

In addition to CN'268 and Gibbs, Dr. Klibanov pointed out four other prior art references that taught a molar ratio of 3:1 to 8:1 of magnesium ions to a tetracycline. (Tr. 494:6–15; DTX-0008; DTX-0009; DTX-0006; DTX-0007.) Of these four references, none is specific to minocycline, but Dr. Klibanov argued that a POSA seeking to make a minocycline formulation would not ignore these references because of minocycline's similarity to other tetracyclines. (Tr. 495:3–12.) None of these references explicitly disclose intravenous formulations, but they disclose parenteral formulations, which encompass intravenous formulations. (Tr. 548:9–20.)

(d) Chemical Similarities Among Tetracyclines

Dr. Klibanov testified that there are "profound structural similarities" among all tetracyclines, particularly with respect to the structure of the lower portion of the tetracycline ring. (Tr. 495:11–21.) Magnesium complexation to tetracyclines has been extensively studied, and it is well known that magnesium binds with all tetracyclines in the lower portion of the B and C tetracycline rings as shown in the figure below—the portion of a tetracycline molecule that does not change across all tetracyclines. (Tr. 495:13–496:15, 479:11–18; DTX-0174.)



On cross-examination, Plaintiffs asked Dr. Klibanov about previous statements he had made about how seemingly small structural differences between two molecules can result in large differences in the properties of the substance, a statement Dr. Klibanov agreed remained true today. (Tr. 531:13–532:20.) Dr. Klibanov then agreed with Plaintiffs that there are three structural differences between minocycline and doxycycline. (Tr. 532:23–533:1.)

(e) Ultimate Opinions on Obviousness of the '802 Patent

Based on an understanding of the chemical structure of minocycline and a familiarity with CN'268 and Gibbs, Dr. Klibanov testified that a POSA should

reasonably expect to successfully create a minocycline formulation with magnesium that improved stability, solubility, and hemolysis. (Tr. 500:24–501:6.) He testified that a POSA following the prior art minocycline's label would have diluted the reconstituted solution to bring the volume to 500–1,000 mL and obtain a final pH of 4.5 to 6, but that same POSA who was familiar with CN'268 and Gibbs would have been motivated to add magnesium at a ratio of up to 8:1 to that prior art minocycline formulation because they would have an understanding that magnesium would improve solubility and enable a lower dosage. (Tr. 501:12–502:9.)

Regarding Claim 1 of the '802 Patent, Dr. Klibanov testified that the prior art minocycline covers all claim elements except the addition of magnesium, but a POSA familiar with CN'268 and Gibbs would have been motivated to add magnesium to the prior art minocycline. (Tr. 504:16–22.) He also testified that the term "injection site hemolysis" in Claim 1 is vague because there is no agreed-upon teaching for how to measure it, but a POSA would nevertheless reasonably expect hemolysis to be reduced in a formulation that included magnesium. (Tr. 505:1–15.) This is because hemolysis reduction is a necessary and "inherent" result of administering a formulation with magnesium and minocycline. (Tr. 505:20–506:10.) Dr. Klibanov also testified that Gibbs taught a magnesium to minocycline molar ratio of up to 8:1, which overlaps with the claimed range of 4:1 in Claim 1. (Tr. 508:3–9.) He also stated that the pH claim limitation in Claim 1 (a pH between 4 and 6) overlaps with the pH in the prior art minocycline when diluted (4.5–6), and the pH levels in the prior art (3–7 in CN'268 and 5–7 in Gibbs). (Tr. 508:18–23.) Dr. Klibanov thus concluded that the

Claim 1 elements about magnesium, reduced hemolysis, a higher molar ratio, and a higher pH level were obvious. (Tr. 507:14–508:2.)

Regarding Claim 7 of the '802 Patent, which narrows the pH range to between 4.5 and 5.5, Dr. Klibanov testified that the prior art references (the prior art minocycline label, CN'268, and Gibbs) teach a pH range that overlaps and encompasses the range in Claim 7. (Tr. 510:1–11.)

Regarding Claim 18 of the '802 Patent, which limits the total administered volume of the composition to 500 mL, Dr. Klibanov testified that Gibbs specifically taught a low injection volume of 5 mL, and the prior art minocycline label also allowed a volume of 500 mL. (Tr. 510:19–511:6.) Based on this prior art, Dr. Klibanov testified that a POSA would have understood that an administration volume of less than 500 mL would have been obvious. (Tr. 511:9–12.)

Dr. Klibanov's ultimate opinion regarding the Asserted Claims of the '802 Patent, based on the prior art references (the prior art minocycline label, CN'268, and Gibbs), was that the Asserted Claims would have been obvious to a POSA. (Tr. 511:13–18.)

(d) Ultimate Opinions on Obviousness of the '105 Patent

Dr. Klibanov first testified that all the opinions he had about the '802 Patent claim elements applied equally to the same claim elements in the '105 Patent. (Tr. 512:4–8, 513:15–515:13.)

Dr. Klibanov also testified about the osmolality element of Claim 1 of the '105 Patent, which teaches an osmolality of less than 500 mOsmol/kg. (*See* PTX-002.) He

testified that the prior art references do not explicitly discuss osmolality, but a POSA would know that the osmolality of the formulation must be near the 300 mOsmol/kg osmolality level of blood, which is within the claimed range of 500 mOsmol/kg. (Tr. 512:17–24, 515:16–21; *see also* DTX-0175.) He stated that the osmolality level of the formulation is "unequivocally dictate[d]" by and an "inevitable result of" the ingredients and concentrations within the formulation. (Tr. 512:25–513:4.)

Dr. Klibanov's ultimate opinion regarding obviousness of the Asserted Claims in the '105 Patent was that all Asserted Claims would have been obvious to a POSA, based on prior art references including the prior art minocycline label, CN'268, and Gibbs. (Tr. 516:10–18.)

2. Dr. Richard Chambers's Testimony on Obviousness

Dr. Chambers testified that he agreed with Dr. Klibanov's assessment of obviousness. (Tr. 618:6–11.) He did not rely on any references other than Gibbs and CN'268 in making this conclusion. (Tr. 676:25–677:7.)

(a) Prior Art Reference Gibbs

Dr. Chambers first testified that a physician reviewing Gibbs, which focuses on doxycycline, would apply conclusions and research about doxycycline to minocycline because the two tetracyclines have similar chemical structures and identical magnesium binding. (Tr. 618:14–22.) Gibbs, which studies an intramuscular formulation, describes the use of oil in its formulation, but Dr. Chambers argued that a POSA would disregard that oil use for an intravenous formulation because injecting oil into a patient's bloodstream would be dangerous. (Tr. 619:1–621:3.) But that same

POSA would still find the remaining information in Gibbs to be helpful because it includes information about how magnesium interacts with doxycycline and, by extension, with minocycline. (Tr. 620:19–622:13.)

When asked about this inclusion of oil on cross-examination, Dr. Chambers testified that oil acts as a "surfactant" in the Gibbs formulation, which increases the solubility of doxycycline. (Tr. 662:2–15.) Gibbs requires an antioxidant to be added to the doxycycline formulation in order to stabilize it. (Tr. 16–19.)

(b) Prior Art Reference CN'268

Dr. Chambers testified about the toxicity and tissue irritability disclosures mentioned in the CN'268 publication. (*See* PTX-14.) CN'268, like Gibbs, studies an intramuscular formulation, and is directed to veterinary use. But he maintained that CN'268 is still relevant to intravenous formulations because high toxicity and irritability at the site of an intramuscular injection would translate to lower toxicity and irritability at the site of an intravenous injection. (Tr. 624:12–23.) He also testified on cross-examination that CN'268 only concerns formulations of doxycycline injection for veterinary use and does not mention minocycline anywhere. (Tr. 666:5–19.)

He also testified that CN'268 describes that magnesium improves a doxycycline formulation by increasing its solubility, improving the pH, and reducing toxicity and tissue irritability. (Tr. 624:5–9.) But all claims in the CN'268 publication require the use of a dissolvent and an antioxidant. (Tr. 670:12–22.) Dr. Chambers then discussed an experiment described in CN'268, which was conducted via

intramuscular administration in pigs, that resulted in no toxicity and other side effects. (Tr. 625:2–5.) But he conceded that CN'268 does not explicitly and directly mention or disclose hemolysis. (Tr. 671:10–12.)

Dr. Chambers concluded that a POSA would be motivated to combine the prior art minocycline, Gibbs, and CN'268 to achieve the claimed formulation and would have a reasonable expectation that developing such an improved formulation would be successful. (Tr. 625:6–22.)

3. Dr. Bruce Friedman's Testimony on Obviousness

(a) Prior Art References

Dr. Friedman repeated his testimony about the issues he witnessed with prior art minocycline. He testified that the problems included injection site tolerability issues, improper pH, and large minimum injection volumes. (Tr. 696:1–3.) As to injection tolerability issues, he explained that a POSA would understand that injection site hemolysis is a risk for any patient that is triggered when injected, and it can create signs and symptoms such as thrombophlebitis, phlebitis, erythema, pain, and potentially skin damage. (Tr. 696:5–25.) As to improper pH, he explained that a lower pH (such as 2–2.8 in prior art minocycline) is more likely to induce injection site hemolysis, a fact he said was supported by two publications: the 2002 Jan-Peter paper and the 1982 Jones paper. (Tr. 697:25–699:7; PTX-179; PTX-181.) As to injection volumes, Dr. Friedman testified that a higher volume of fluid administered to a patient (such as a minimum 500 mLs in prior art minocycline) means increased cell contact and, therefore, increased risk of intolerability. (Tr. 699:8–700:1.)

Dr. Friedman cited several publications to support his opinion that there were known issues with the prior art minocycline. First, a 1995 Klein paper includes research on only doxycycline because all other parenteral tetracyclines (such as minocycline) were associated with thrombophlebitis and hepatic toxicity (liver damage). (Tr. 700:2–23; PTX-182.) Klein teaches that using minocycline carries many risks, and a physician administering it to a patient with a bacterial infection needs to be careful. (Tr. 701:24–702:9.) Second, Dr. Friedman cited a 1996 Sweetana paper. (*See* PTX-233.) Sweetana measures pH from the reconstituted solution, and the prior art minocycline had one of the lowest pHs of several other formulations studied in the Sweetana paper. (Tr. 702:11–17, 703:9.) Dr. Friedman did not cite to any article that showed reduced hemolysis of Minocin as compared to the prior art minocycline. (Tr. 753:4–7.) Nor did he discuss the Gibbs reference or the CN'268 reference. (Tr. 762:20–763:4.)

(b) Secondary Considerations

Dr. Friedman also relied on his own experience to support his opinion. At the burn and wound center where he is employed, he saw many patients who were treated with prior art minocycline and had hemolysis symptom such as skin breakage and damage, which would then extend the length of their stay. (Tr. 704:5–14.) But he continued to use prior art minocycline because they had few other options to treat a bacterial infection. (Tr. 704:25–705:7.) Dr. Friedman testified that minocycline was especially effective against bacterial infections as opposed to other tetracyclines such as doxycycline because of the addition of nitrogen on the second methyl ring, which

changes the minocycline's chemical structure to afford it unique features such as a lower likelihood of resistance patterns. (Tr. 706:11–25.) Because of this difference, Dr. Friedman testified, a POSA would not extrapolate disclosures and findings about doxycycline and apply them to minocycline. (Tr. 707:1–10.)

Based on this testimony, Dr. Friedman concluded that there was a long-felt but unmet need for an improved intravenous formulation of minocycline that reduced injection site tolerability issues. (Tr. 708:18–709:3.) He testified that there were "valiant efforts" to improve prior art minocycline, but no one was successful. (Tr. 709:17–19.) A POSA could not try to increase the pH of the prior art minocycline because it would lead to solubility issues, nor could a POSA decrease the minimum injection volume because lower pH required higher injection volumes to avoid tolerability issues. (Tr. 709:21–710:7; PTX-175.)

Dr. Friedman testified that the Minocin product was a "much-needed breakthrough." (Tr. 711:13–14.) Minocin added magnesium at a 5:1 molar ratio, and had a lower pH and injection volume than prior art minocycline. (Tr. 711:1–8.) Minocin was effective against several bacteria that other antibiotics could not treat, and it reduced the risk of injection site hemolysis, allowing it to be routinely used to treat patients. (Tr. 711:11–23.)

On cross-examination, Dr. Friedman was questioned about the pH element of the minocycline formulations. Both the prior art minocycline and Minocin's product labels require dilution before the formulation is administered using diluents such as Lactated Ringer's or a normal saline. Lactated Ringer's is an option to use as a diluent

but not the standard of care, and normal saline was the recommended standard of care. (Tr. 722:5–724:24.) This is because Lactated Ringer's is a formulation used primarily to restore fluids to patients low on volume due to trauma or burns, not a diluent for pharmaceuticals. (Tr. 765:18–766:2.) If Lactated Ringer's was used as a diluent in an administration of the prior art minocycline (although it would be highly unlikely for a POSA to use that diluent), the pH of the diluted solution would be 4.5 to 6.0. (Tr. 728:3–729:7.)

4. Dr. Tina deVries Testimony on Obviousness

(a) Response to Defendant's Obviousness Arguments

Dr. deVries testified about the Gibbs and CN'268 references that Dr. Chambers and Dr. Klibanov discussed. First, Gibbs was considered by the patent examiner during prosecution of the patents-in-suit. (Tr. 809:21–24; PTX-132.) Gibbs does not disclose any examples of minocycline, nor any attempts to make a minocycline formulation; instead, Gibbs only studies doxycycline. (Tr. 809:6–810:8.) The Gibbs compositions were administered intramuscularly without any examples of intravenous administration. (Tr. 810:20–25.) Dr. deVries explained that a POSA would not extrapolate this data and apply it to intravenous minocycline formulations. First, a POSA would want to see additional data on minocycline specifically, especially in the context of the prior art references she previously testified about. (Tr. 810:9–15.) Second, a POSA could not extrapolate findings about intramuscular formulations to intravenous formulations because intravenous formulations must be administered as a solution to avoid precipitation, whereas an intramuscular injection

does not have to be a solution and can accommodate another phase such as an oil to help solubilize the formulation. (Tr. 811:3–812:2.) Gibbs also teaches an antioxidant was necessary to stabilize doxycycline, without any discussion or implication that magnesium could improve stability or solubility. (*Id.* 812:18–24.) But Gibbs does explain that an antioxidant is optional if a POSA wants to ensure stability. (Tr. 896:2–12.) Although Gibbs discusses an 8:1 ratio of magnesium to drug, it does not discuss the significance of the molar ratio of metal cations. (Tr. 812:25–813:2, 845:25–846:4.) Accordingly, Dr. deVries testified that a POSA would not have considered the Gibbs reference to be relevant. (Tr. 813:6–8.)

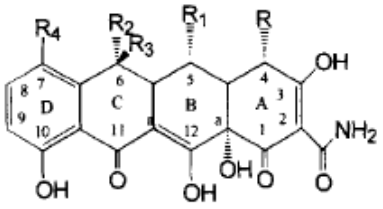
The CN'268 reference studies an intramuscular doxycycline injection for veterinary use. (Tr. 813:13–814:2.) CN'268 does not disclose anything about either minocycline or intravenous formulations. (Tr. 813:13–14, 814:3–5.) Like Gibbs, CN'268 taught that an antioxidant is necessary to stabilize doxycycline, rather than magnesium. (Tr. 814:25–815:7.) Nor does CN'268 discuss the significance of a higher molar ratio. (Tr. 815:8–10.) CN'268 does discuss magnesium. (Tr. 845:19–21.) Dr. deVries agreed that CN'268 was not considered by the patent office during the Minocin approval process. (Tr. 846:5–10.)

Dr. deVries testified about the other prior art references Dr. Klibanov discussed (Weidenheimer, 1967; Beutel, 1972; Akazawa, 1974; Noseworthy, 1976). She explained that none of those references mentioned minocycline at all, all taught the addition of other excipients to stabilize the formulation, and all studied intramuscular formulations. (Tr. 815:14–816:5.) She testified that a POSA seeking to

make a minocycline solution for intravenous administration would not have learned anything from these references. (Tr. 816:10–13.)

(b) Chemical Structures of Minocycline and Doxycycline

Dr. deVries testified that doxycycline is not a 7-dimethylamino-tetracycline, which the claims of the patents-in-suit are directed to. (Tr. 821:7–16.) Doxycycline and minocycline have three structural differences in the upper group of the molecule, as indicated in R1, R2, and R4 of Rows D and E in the below figures from the 1998 Nelson reference:



Tetracycline Natural Products	R	R_1	R_2	R_3	R_4
A. Chlortetracycline	$N(CH_3)_2$	H	CH_3	H	Cl
B. Oxytetracycline	$N(CH_3)_2$	OH	CH_3	OH	H
C. Tetracycline	$N(CH_3)_2$	H	CH_3	H	H
Tetracycline Semi-synthetic Compounds					
D. Minocycline	$N(CH_3)_2$	H	H	H	$N(CH_3)_2$
E. Doxycycline	$N(CH_3)_2$	OH	CH_3	H	H
F. Methacycline	$N(CH_3)_2$	OH	$= CH_2$	-	H

(Tr. 821:22–822:5; PTX-151.) Although it is true that magnesium only binds to the lower region of the tetracycline structure, the Nelson reference says other studies show that the upper group is also implicated. (Tr. 822:6–15.) The Nelson reference also teaches that modification of the upper group may "drastically alter" chemical attributes of a tetracycline, which can lead to changes in solubility. (Tr. 823:2–7.) Accordingly, Dr. deVries explained, a POSA would understand that the three structural differences between minocycline and doxycycline in the upper region could significantly affect how the molecules interact with metal cations. (Tr. 823:22–824:1.)

Dr. deVries also testified that the 1974 Barringer reference teaches that the differences between minocycline and doxycycline, including solubility, are attributed

specifically to the presence of a 7-dimethylamino group in minocycline that does not appear in doxycycline. (Tr. 824:6–19; PTX-152.)

Based on these references, Dr. deVries concluded that a POSA would not have been motivated to attempt minocycline formulations based on prior art references that only disclose information on doxycycline. (Tr. 825:1–4.) A POSA attempting such a strategy would not have had a reasonable expectation of success. (Tr. 825:5–8.)

(c) Secondary Consideration #1: Teaching Away

Dr. deVries testified on objective teaching away in prior art references. She began by testifying about her own 2006 publication. (PTX-134.) Her experiments involved an aqueous solution of minocycline with metal cations (such as magnesium) and an increased pH, which resulted in immediate formation of insoluble particles (which she described as "suspension"). (Tr. 775:4–19.) The molar ratio of metal cations to minocycline used in her experiments ranged from 1:3 to 3:1. (Tr. 775:20–23.) Thus, she testified that her experiments taught that a molar ratio up to 3:1 became insoluble when a base was added, at which point the formulation was at a pH level near 4. (Tr. 776:4–7, 782:12–18.) That a higher molar ratio of magnesium to minocycline did not result in solubility issues was therefore surprising to Dr. deVries, especially in combination with other literature warning about the combination of metal cations with minocycline. (Tr. 776:24–777:15.)

Dr. deVries testified about this other literature. First, a 1998 Yalkowsky paper explains how hemolysis and phlebitis are major adverse effects of intravenous administration. (Tr. 780:15–781:1.) Next, a 1974 Barringer paper that studies the

solubility of minocycline at a 2:1 molar ratio of magnesium ions resulted in a seven-fold reduction in solubility in the presence of magnesium at a pH of 6.5. (Tr. 782:23–783:20; PTX-152.) Dr. deVries testified that a POSA reading Barringer would learn that calcium or magnesium should not be included in a minocycline formulation because it would react with minocycline and precipitate[13] out of solution. (Tr. 783:21–784:1.) She testified that this information is applicable to intravenous solutions, which must be solutions for administration, so the potential for precipitation and insolubility is important. (Tr. 788:7–14.) With this understanding, she testified that the inventors of the patents-in-suit surprisingly found that adding magnesium into a minocycline formulation at a 5:1 ratio was able to result in a solution suitable for intravenous administration. (Tr. 788:15–789:4.)

Third, a 1983 Berthon reference studied the interaction between magnesium and minocycline. (Tr. 789:5–11; PTX-158.) This reference found the presence of precipitation in fluids that combined magnesium and minocycline at a higher pH. (Tr. 789:17–790:3.) She stated that a POSA would have learned from Berthon to avoid combining magnesium with minocycline for an intravenous solution. (Tr. 790:4–8.) Fourth, a 1976 Allen reference conveyed the same message. (Tr. 790:20–23.) The Allen reference surveyed the treatment and use of minocycline in a clinic, concluding that minocycline chelates with metal cations with a loss of solubility. (Tr. 790:12–19; PTX-157.)

[13] "Precipitation" is a process by which a substance is "separated from a solution by the action of a reagent so that a precipitate forms. *Precipitation*, Taber's Medical Dictionary Online (24th ed.).

Fifth, a 1982 Pawelczyk reference considered by the FDA investigates the stability of minocycline in aqueous solutions within a broad pH range. (Tr. 791:9–22; PTX-133.) DeVries testified that Pawelczyk taught that the degradation of minocycline increased at a pH of 4 to 6, meaning that a POSA reading Pawelczyk would learn to keep the pH of a minocycline formulation between 2 and 3 to maintain stability. (Tr. 793:4–20.) Pawelczyk also studies the effect of metal ions on the degradation rate of minocycline, which showed that the addition of magnesium did not have any distinct effect on the rate of degradation versus a formulation without magnesium. (Tr. 794:3–13.) Pawelczyk was pre-formulation work reporting data on experiments, not attempting to create a pharmaceutical formulation. (Tr. 850:25–851:7.)

In summary, Dr. deVries testified that these five references would teach a POSA away from the claimed invention in the patents-in-suit. (Tr. 795:1–3.) This is because the reference taught a POSA to avoid formulating solutions of minocycline over a pH of 4, avoid adding metal cations, and avoid adding high molar ratios of metal cations to minocycline. (Tr. 4–11.)

(d) Secondary Consideration #2: Length of Intervening Time

Dr. deVries testified that the length of intervening time between the prior art minocycline (1973) and the patents-in-suit (2010) is evidence of non-obviousness. (Tr. 799:8–13.) She cited several publications to support her opinion that no one could determine how to fix the prior art minocycline for almost forty years. (Tr. 14–16.) Dr. deVries testified in particular about the pH of the prior art minocycline, which is 2 to

2.8 for the reconstituted solution and 2.5 to 4 for the diluted solution. (Tr. 796:19–797:2.) The Broadhead article teaches an avoidance of a pH less than 3, which may cause pain and phlebitis. (Tr. 796:3–15; PTX-225.) A 1998 Kokotis article found that an acidic drug with a pH below 4.1 could damage a vein's inner layer. (Tr. 797:7–17; PTX-185.) The 2002 Jan-Peter article stated that the risk of hemolysis, precipitation, phlebitis, and pain is well-known to be higher at a lower pH level. (Tr. 797:21–798:4; PTX-179.) Dr. deVries testified that a POSA would be aware of all these publications and, in view of that, would know that the pH of the prior art minocycline was so low to maintain solubility and stability. (Tr. 798:11–22.) No changes were made to the prior art minocycline formulation until Minocin was approved forty years later because no one knew how to improve it. (Tr. 799:8–16.)

On cross-examination, Dr. deVries was asked about the Broadhead reference. She testified that Broadhead stated a parenteral product should have a pH close to physiological range (approximately 7.4) unless precluded by solubility or stability problems, but a wide pH range can be tolerated when administered intravenously. (Tr. 852:19–853:15.) Broadhead also taught that hypertonic solutions (osmolality above 500) were preferable to hypotonic solutions (a lower osmolality) because of a risk of hemolysis associated with hypotonic solutions. (Tr. 854:23–855:15.) Dr. deVries did not agree that Broadhead was thus teaching that increased osmolality reduced hemolysis. (Tr. 855:3–7.) Dr. DeVries also did not agree that hypotonic formulations are included in the '105 Patent. (Tr. 857:19–21.)

(e) Secondary Consideration #3: Unexpected Results

Dr. deVries disagreed with Defendant's argument that CN'268 and Gibbs were the closest prior art and should have been used as comparators. (Tr. 800:25–801:3.) Both references were void of any data about minocycline formulations, did not concern intravenous formulations, and taught the addition of stabilizers and solubilizers. (Tr. 801:4–9.) Dr. deVries testified that the inventors of the patents-in-suit had "unexpected and surprising results." (Tr. 801:16.) They "found that by adding high molar ratios of magnesium cations greater than 3 to 1, they were able to successfully create an aqueous solution of minocycline . . . suitable for intravenous administration" with a composition and administration pH over 4 for all diluents. (Tr. 801:17–24.) And this formulation did not have significant solubility or stability issues, was able to be administered at a volume less than 500 mLs, and reduced injection site hemolysis. (Tr. 801:17–802:2.) Dr. deVries testified that she was surprised by these results because they were the exact opposite of her findings in the 2006 publication. (Tr. 802:3–17.)

Dr. deVries stated that the FDA reviewed all experimental data generated by the inventors. (Tr. 802:13–15.) The FDA concluded that those experiments showed that the addition of magnesium to minocycline improved stability and solubility at higher pH values, had the potential to reduce injection site hemolysis compared to the prior art minocycline, and enabled administration at a smaller volume. (Tr. 804:8–22.) The FDA thus was saying that the studies and data showed that the new formulation improved the prior art minocycline. (Tr. 806:6–14.)

In summary, Dr. deVries affirmed that the results of the inventors' experiments showed that compositions that meet the limitations of the Asserted Claims are sufficiently stable and soluble for intravenous administration and reduce the risk of injection site hemolysis relative to compositions that do not include magnesium. (Tr. 807:7–17.) She testified that the unexpected results were due to the claimed features of the invention, including a molar ratio of magnesium to minocycline of greater than 3:1. (Tr. 807:18–22.) Dr. deVries concluded that there is a nexus between the unexpected results and the claimed invention, which is objective evidence of non-obviousness. (Tr. 807:23–808:3.)

Dr. deVries concluded that a POSA would not have been motivated to combine these prior art references with the prior art minocycline because they did not discuss minocycline, intravenous formulations, or molar ratios, and they discussed the presence of additional solubilizing agents not in the Asserted Claims. (Tr. 817:11–25.) She added that even if a POSA was so motivated, the POSA could not have had a reasonable expectation of success in achieving the claimed invention. (Tr. 818:17–21.)

5. Round Four: Defendant's Response on Secondary Considerations

(a) Dr. Klibanov's Response

In Round Four of argument, Dr. Klibanov testified in response to Plaintiffs' secondary considerations arguments. First, he responded to Dr. deVries's teaching away arguments. He explained that in order to teach away, a reference must criticize, discredit, or otherwise discourage a POSA from making a claim, which he testified

Dr. deVries had not done for the pH, magnesium, or molar ratio claims. (Tr. 911:16–912:12.) Dr. Klibanov also discussed Dr. deVries's testimony about the Barringer article. He disagreed that it teaches away from intravenous formulations with high concentrations of metal cations, because the article concerns oral absorption, not aqueous solutions or intravenous formulations. (Tr. 912:13–915:1.) Accordingly, he testified, Barringer would not have taught a POSA away from creating an aqueous solution of minocycline with a high molar ratio of magnesium at a pH above 4. (Tr. 916:5–22.) But on cross-examination, he agreed that Barringer did teach that the minocycline and magnesium complex can precipitate from an aqueous solution depending on the pH value, becoming unsuitable for intravenous administration. (Tr. 920:20–921:23.) Dr. Klibanov also disagreed with Dr. deVries that a POSA would have expected such a formulation to have stability and solubility issues based on the prior art. (Tr. 916:23–917:5.)

Dr. Klibanov's ultimate opinions on obviousness were: (1) there were no surprising and unexpected results; (2) no references taught away from the claimed invention; (3) there was no long-felt need met by the formulation; and (4) copying did not suggest the claims were innovative. (Tr. 917:6–19.)

(b) Dr. Chambers's Response

In round four of argument, Dr. Chambers testified that Minocin did not change the use, efficacy, and safety of the prior art minocycline. (Tr. 908:14–21.) Both formulations treated the Acinetobacter bacteria, and the prior art minocycline could have continued to have been used to treat that bacteria if it had not been removed

from the market. (Tr. 909:2–15.) He again concluded that the Asserted Claims in the '105 Patent and the '802 Patent are obvious. (Tr. 909:19–23.)

F. Rounds Two and Three: Testimony on Section 112

This Section discusses both parties' testimony on the Section 112 arguments of invalidity, including lack of enablement and lack of written description. This testimony was presented in Rounds Two, Three, and Four.

1. Dr. Alexander Klibanov's Testimony on Section 112

Dr. Klibanov testified as to his invalidity opinion regarding lack of enablement and lack of written description of the patents-in-suit. This opinion applied only to the pH claims asserted: (1) Claim 1 of the '802 Patent requiring a pH between 4 and 6, and (2) Claim 1 of the '105 Patent requiring a pH between 4 and 7. (Tr. 525:18–526:1.) Dr. Klibanov testified that based on the disclosures in the patents-in-suit, a POSA would not be able to make formulations suitable for intravenous administration at the pH levels claimed. (Tr. 527:11–14.) This is because under some conditions that would fall within the scope of the claims, minocycline would be insoluble and thus unsuitable for administration to a patient. (Tr. 526:12–527:14.)

2. Dr. Richard Chambers's Testimony on Section 112

Dr. Chambers testified that the '802 Patent specification suffers from lack of written description and enablement because it does not define, measure, or report injection site hemolysis, and therefore does not teach a POSA how to reduce it. (Tr. 600:9–17.)

Dr. Chambers testified that he was not aware of any report that the prior art minocycline was withdrawn from the market due to problems of injection site tolerability. (Tr. 607:21–24.) Several changes were made with the new Minocin formulation, including the addition of magnesium and an added base to adjust the pH. (Tr. 608:2–6.) But he stated neither safety nor efficacy was improved with Minocin because the product label had not changed, and the steps for preparing the product for administration had also not changed. (Tr. 608:7–609:2.) Dr. Chambers's testimony followed strict adherence to the product labels. For instance, he stated that the '105 Patent covered an osmolality range from 0 to 500 because the label stated an osmolality "less than about 500 mOsmol/kg," and that the '802 Patent covered a volume administration range of 0 to 500 mL because the label did not specify a lower limit. (Tr. 610:4–611:3, 614:6–615:15.) In his opinion, an osmolality or volume level that was too low within those wide ranges could be unsafe and harmful to a patient. (Tr. 610:10–22, 614:15–18.) Because no lower limits are specified, Dr. Chambers testified that there was a lack of written description and enablement as to these two matters. (Tr. 615:12–15.)

But on cross-examination, Dr. Chambers testified that a POSA would be able to adjust the volume of administration to a therapeutically effective amount by looking at the label. (Tr. 649:18–650:15.) Similarly, a POSA would be familiar with the diluents listed on the label and would be able to select and use an appropriate diluent to ensure that the administered solution has an osmolality of less than 500 mOsmol/kg. (Tr. 650:19–654:20.)

3. Dr. Bruce Friedman's Testimony on Section 112

Dr. Friedman testified in response to Defendant's claim of lack of written description and lack of enablement as to the administration volume in the '802 Patent and osmolality in the '105 Patent and the injection site hemolysis claims.

Dr. Friedman first testified that the total volume of the administered composition in the '802 Patent was 500 mL, and this referred to the diluted solution. (Tr. 713:18–23.) But a POSA would know that some embodiments of the formulation could be formulated with much lower volumes and could adjust the formulation accordingly. (Tr. 713:25–714:13.) A POSA would never administer such a low formulation as to make the drug toxic or no longer therapeutically effective. (Tr. 714:14–18.) It is true that the '802 Patent does not specify a lower limit of volume, but a POSA would know how much to decrease the volume of a formulation to avoid toxicity. (Tr. 746:20–747:2.) Even though the '802 Patent does not have any examples of tests conducted at less than 50 mL of volume, a POSA would not have to conduct experiments to determine how low of a volume would be appropriate because they would know based on their experience. (Tr. 746:10–748:17.) Dr. Friedman also testified on cross-examination that there were several articles submitted to the FDA on the use of minocycline (without magnesium) at a volume between 100 mL and 500 mL. (*Id.* 754:2–759:5.) Ultimately, Dr. Friedman testified that he believed the '802 Patent was enabled and supported by adequate written description. (Tr. 715:4–5.)

Dr. Friedman then testified that the injection site hemolysis claims were not indefinite because a POSA would know what injection site hemolysis is, how it's

related to tolerability issues, and that it will be reduced in any patient who is treated with Minocin because it is a property of the formulation. (Tr. 716:7–16.) A POSA would know that hemolysis would be reduced in the Minocin formulation or the ANDA product because the POSA would be able to see a higher pH range and a reduced volume due to the addition of magnesium at an appropriate molar ratio. (Tr. 768:15–769:3.) On cross-examination on the hemolysis issue, Defendant pointed out several tests mentioned in the '802 Patent that resulted in an insoluble formulation and insinuated that the formulation could not be administered and could not reduce hemolysis. (Tr. 736:18–739:4.) Dr. Friedman also testified on cross-examination that the '802 Patent does not inform a POSA of where injection hemolysis starts and stops in the vein, nor does it teach how to measure the rate or extent of hemolysis in the bloodstream. (Tr. 742:12–743:10.)

Finally, Dr. Friedman testified that a POSA would know to avoid the lower limit of osmolality. A POSA would know that there is a lower limit that would affect the therapeutic effectiveness of a formulation and cause substantial tissue damage. (Tr. 717:1–10.) He testified that the osmolality element of the '105 Patent does not, therefore, suffer from lack of enablement or written description because the label specifies an osmolality less than 500 mOsmol/kg, and a POSA would know how to adjust certain parameters of the formulation to intravenously administer a therapeutic amount of the formulation at an acceptable osmolality. (Tr. 717:11–25.)

4. Dr. Tina deVries's Testimony on Section 112

Dr. deVries testified that a POSA reading the patents-in-suit's specifications would understand how to make and use the claimed invention across the full pH range specified (4 to 7 in the '105 Patent and 4 to 6 in the '802 Patent). (Tr. 831:15–20.) She testified that the claimed invention works at every pH value included in the scope of the Asserted Claims, and that Defendant has not pointed to any pH value at which the claimed invention does not work. (Tr. 832:9–19.)

As to osmolality, Dr. deVries testified that a POSA would know how to measure osmolality and make the claimed composition at the instructed osmolality of less than 500 mOsmol/kg. (Tr. 832:21–25.) A POSA would not consider reducing osmolality at a level close to 0. (Tr. 834:4–6.) And Defendant has not pointed to any osmolality value at which the claimed invention would not work or would be unsuitable for intravenous administration. (Tr. 834:7–11.)

As to hemolysis, Dr. deVries testified that a POSA would understand, after reviewing the hemolysis data in the specifications, that a formulation within the scope of the Asserted Claims would reduce hemolysis. (Tr. 835:1–5.) A POSA would not be concerned that the hemolysis experiments in the specifications were conducted in vitro versus on human patients. (Tr. 835:14–18.) The FDA knew that the inventors used in vitro tests as a model for hemolysis. (Tr. 836:7–11.) Specifically, Dr. deVries stated that the inventors' use of rabbit blood cells in the experiment was a good thing because those cells are very sensitive, so any improvement or benefit that can be seen in rabbit ear blood cells will mean that the inventors can reliably assume that the same benefit will be seen in other cells. (Tr. 836:23–637:13.) On cross-examination,

Defendant examined Dr. deVries about these rabbit blood cell tests. (*See* Tr. 864:11–872:8.) Defendant questioned the results of three in vitro tests that the inventors conducted and Plaintiffs relied on, even though these tests only showed "minor differences." (Tr. 869:4–16.) Dr. deVries did not agree with how Defendant construed this experiment. (Tr. 869:17–18.)

V. CONCLUSIONS OF LAW

In patent infringement cases, the patentee bears the burden of proving infringement of every claim by a preponderance of the evidence. *Creative Compounds, LLC v. Starmark Lab'ys*, 651 F.3d 1303, 1314 (Fed. Cir. 2011) (quoting *SRI Int'l v. Matsushita Elec. Corp.*, 775 F.2d 1107, 1123 (Fed. Cir. 1985)). If the patentee does not meet that burden, "the patentee loses regardless of whether the accused comes forward with any evidence to the contrary." *Id.*

An accused infringer can respond by asserting affirmative defenses: (1) non-infringement; (2) invalidity of the patent on any ground specified as a condition for patentability (e.g., obviousness or lack of novelty); or (3) invalidity of the patent or any claim in suit for failure to comply with any requirement of § 112 (e.g., indefiniteness, lack of enablement, or lack of written description). 35 U.S.C. § 282(b). A patent is presumed valid, but a defendant asserting an invalidity defense may rebut that presumption by proving invalidity by a heightened standard of clear and convincing evidence. *Id.* § 282(a); *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 97 (2011). Then, in response to an invalidity for obviousness defense, the plaintiff can rebut by presenting secondary considerations establishing objective evidence of non-

obviousness by a preponderance of the evidence. *See Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1053 (Fed. Cir. 2016). Secondary considerations of non-obviousness can include (1) commercial success, (2) copying, (3) long-felt but unmet need, (4) skepticism or disbelief, (5) positive recognition, and (6) unexpected results. *In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998). But evidence of secondary considerations does not always overcome a strong showing of obviousness. *Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008).

Plaintiffs allege that Defendant has infringed on Claims 1, 7, and 18 of the '802 Patent and Claim 27 of the '105 Patent. Defendant argues that it has not infringed and, even if it had infringed, the patents-in-suit are invalid for obviousness, indefiniteness, lack of enablement, and lack of written description. Plaintiffs respond by presenting several secondary considerations to argue non-obviousness. The Court's analysis of each argument follows.

A. Infringement

1. Direct Infringement

Plaintiffs argue that Defendant's marketing and use of its ANDA product will indirectly infringe the patents-in-suit. But to prevail on an indirect infringement claim, a plaintiff must first prove direct infringement by a third party. *See Aro Mfg. Co. v. Convertible Top Replacement Co.*, 365 U.S. 336, 341 (1961); *Limelight Networks, Inc. v. Akamai Techs., Inc.*, 572 U.S. 915, 920–21 (2014). A party directly infringes when it "without authority makes, uses, offers to sell, or sells any patented invention, within the United States . . . ." 35 U.S.C. § 271(a). To determine

infringement, the court must compare the "asserted claim as properly construed" to the "accused method or product." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1581–82 (Fed. Cir. 1996); *see also Mas-Hamilton Grp. v. LaGard, Inc.*, 156 F.3d 1206, 1211 (Fed. Cir. 1998). To prevail on direct infringement claims, the plaintiff must show infringement of every claim limitation by a preponderance of the evidence. *See, e.g.*, *Bayer AG v. Elan Pharm. Rsch. Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000).

To prove direct infringement, Plaintiffs must show that "if [Defendant's ANDA product] were put on the market, if would infringe the [patents-in-suit]." *Genentech, Inc. v. Sandoz Inc.*, 55 F.4th 1368, 1379 (Fed. Cir. 2022) (quoting *Vanda Pharms. Inc. v. W.-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1129 (Fed. Cir. 2018)). This determination requires " 'consideration of all the relevant evidence,' including the proposed label's instructions and physician practice." *Id.* (quoting *Ferring B.V. v. Watson Lab'ys, Inc.-Fla.*, 764 F.3d 1401, 1408 (Fed. Cir. 2014). Courts may also consider the ANDA product itself, any materials the generic drug company submitted to the FDA, and "other pertinent evidence provided by the parties." *Glaxo, Inc. v. Novopharm, Ltd.*, 110 F.3d 1562, 1570 (Fed. Cir. 1997). In short, courts are permitted to—and regularly do—consider relevant evidence outside the ANDA product's label to evaluate whether the product directly infringes the claims. *See Genentech*, 55 F.4th at 1379–80; *Ferring B.V.*, 764 F.3d at 1409–10; *Par Pharm., Inc. v. Eagle Pharms., Inc.*, 44 F.4th 1379, 1383–84 (Fed. Cir. 2022) ("If the ANDA specification does not speak clearly and directly to the question of infringement, courts may look to other relevant evidence . . . to assess whether a proposed product will infringe.").

Plaintiffs argue that Defendant is liable for indirect infringement because a physician using the generic ANDA product would directly infringe on the patents-in-suit. They contend that because the allegedly infringing generic product's label instructs a physician on how to use the product, that physician's act of following the ANDA product label would meet the claim elements at issue in this case, thus directly infringing on the patents-in-suit. (Dkt. 252 ¶¶ 102, 151; Dkt. 253 ¶ 30.) Defendant argues that Plaintiffs have failed to prove that the ANDA product directly infringes on the osmolality element of the '105 Patent and the injection site hemolysis element of the '802 Patent. (Dkt. 250 at 21–27; Dkt. 254 at 11–15; Dkt. 255 ¶¶ 46–48.)

(a) A Physician Using Defendant's ANDA Product Will Directly Infringe on Claim 27 of the '105 Patent.

Claim 27 of the '105 Patent depends on Claim 1, which specifies that administering Minocin according to the specified instructions will cause an osmolality of less than 500 mOsmol/kg. (PTX-002.) Neither the Minocin label nor the ANDA label explicitly mentions osmolality. Plaintiffs argue that even though neither label explicitly mentions osmolality, a physician following the ANDA label nevertheless infringes because the product will inevitably have an osmolality of less than 500 mOsmol/kg due to its chemical composition. (Dkt. 252 ¶¶ 135–38.) Plaintiffs cite "numerous direct measurements of osmolality" of the ANDA product that they performed, all of which resulted in an osmolality of less than 500 mOsmol/kg; thus, Plaintiff argues, the ANDA product is within the scope of the '105 Patent's osmolality claim. (*Id.* ¶ 139.) Defendant counters that Plaintiffs' experiments used a different composition volume (10 mL) than what was specified in the ANDA (5 mL), so the test

results cannot show infringement of the osmolality limitation. (Dkt. 255 ¶¶ 43–44.) But Plaintiffs insist that they did rely on experimental data using 5 mL of composition. (Dkt. 251 at 11.)

Osmolality is a property of a composition, meaning it is measured through simple calculations based on the ingredients in a composition. *See Osmolality*, Taber's Medical Dictionary Online (24th ed.). Accordingly, a POSA looking at the amounts of ingredients in a product described on its label would be able to discern the osmolality of the solution. (Dkt. 252 ¶ 138; Tr. 235:22–236:20, 651:18–21.) The parties agree on the following three facts: (1) osmolality is a property of the composition that can be calculated by looking at the ingredients on the label; (2) the osmolality standard of care is a level below 500 mOsmol/kg; and (3) the Minocin and ANDA product labels are identical and use identical ingredients at identical amounts, as required by the FDA.

Thus, a physician following the ANDA label will perform the same exact process as a physician following the Minocin label. There is no evidence that a physician using Defendant's ANDA product will deviate from the standard of care; accordingly, a physician administering either product will ensure that the osmolality level is less than 500 mOsmol/kg. Just as administering Minocin will inevitably lead to an osmolality of less than 500 mOsmol/kg, administering the ANDA product will also inevitably lead to an osmolality of less than 500 mOsmol/kg. Defendant does not dispute this.

Defendant yet argues that it does not infringe the osmolality element of the '105 Patent because osmolality is not explicitly stated on the Minocin product label. But it does not need to be stated on the label for Defendant to infringe. Osmolality is a property of the composition, as both parties agree. It will be infringed if the physician follows the ANDA label because of the amounts of ingredients stated on the label. *See Sanofi v. Watson Lab'ys Inc.*, 875 F.3d 636, 644–46 (Fed. Cir. 2017) ("The content of the label in this case permits . . . . the required factual inferences about intended effects to rest on circumstantial evidence in appropriate circumstances."); *see Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1368–69 (Fed. Cir. 2017) ("When the alleged inducement relies on a drug label's instructions, '[t]he question is not just whether [those] instructions describ[e] the infringing mode, . . . but whether the instructions teach an infringing use *such that* we are willing to infer from those instructions an affirmative intent to infringe the patent.' " (quoting *Takeda Pharm. U.S.A., Inc. v. W.-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015))); *GlaxoSmithKline LLC v. Teva Pharms. USA, Inc.*, 7 F.4th 1320, 1334 n.6 (Fed. Cir. 2021) ("[W]hen a label instructs or teaches an infringing use, it can be considered evidence of intent to encourage that use.").

Defendant also argues that there would be no direct infringement because Plaintiffs did not rely on any experimental data or osmolality measurements for a product reconstituted with 5 mL of water. (Dkt. 250 at 22.) Defendant focuses on Dr. deVries's testimony, arguing that she admitted to using 10 mL of water in reconstitution and guessed that a 5 mL measurement would "double." But Defendant

mischaracterizes the tests Plaintiffs conducted and Dr. deVries's testimony. All experimental osmolality measurements for Minocin resulted in an osmolality of less than 500 mOsmol/kg, thereby within the claim element of the '105 Patent. And all used a composition of 5 mL of water for reconstitution. Dr. deVries never admitted that she used 10 mL in an experiment; rather, she explained that a 10 mL sized vial was used. She never agreed that she relied on data that used 10 mL of water but instead relied on data that used 5 mL of water.

There is plenty of evidence that Plaintiffs relied on data using 5 mL reconstitution volume. (*See* PTX-197; PDX-2039; PTX-042; DTX-075.) Each of these data resulted in an osmolality of less than 500 mOsmol/kg. Dr. deVries's passing reference to the osmolality approximately doubling when asked about a report that she did not rely on does not change that. And at bottom, it is undisputed that the osmolality standard of care is less than 500 mOsmol/kg, an osmolality level that is explicitly stated in the '105 Patent, and an osmolality level that will necessarily be reached when a POSA uses Defendant's ANDA product with its specified 5 mL of water. Accordingly, a POSA who uses the ANDA product will directly infringe on Claim 27 of the '105 Patent.

(b) A Physician Using Defendant's ANDA Product Will Directly Infringe on Claims 1, 7, and 18 of the '802 Patent.

Defendant does not dispute that a physician following its ANDA label meets most of the limitations in the Asserted Claims. First, Claim 1 of the '802 Patent claims a method of treating a bacterial infection by intravenously administering a therapeutically effective amount of the composition. (PTX-1.) The ANDA label also

instructs the treatment of bacterial infections through an intravenous route. (PTX-042.) Second, Claim 1 claims an aqueous composition consisting of minocycline, magnesium, and a base. So does the ANDA label. Third, Claim 1 claims a molar ratio of magnesium to minocycline at a molar ratio greater than 4:1. The ANDA label instructs a molar ratio of 5:1, which meets the claimed greater than 4:1 ratio. Fourth, Claim 1 claims a pH of 4 to 6 for the reconstituted solution, and Claim 7 claims a pH of 4.5 to 5.5 for the reconstituted solution. The ANDA label instructs a reconstituted pH of 4.5 to 5.0, which fits within both Claims 1 and 7. Finally, Claim 18 of the '802 Patent claims a total admixture volume of less than 500 mL. The ANDA label teaches a total admixture volume of 100 mL to 1,000 mL. A physician who uses 501 mL to 1,000 mL when administering the ANDA label would not, therefore, meet Claim 18, as Dr. deVries testified. But Dr. Friedman, Dr. deVries, and Dr. Chambers all testified that a lower injection volume is beneficial and preferred. A POSA would never choose to administer more volume (over 500 mL) if less volume (less than 500 mL) is sufficient. Accordingly, a physician following the ANDA label would infringe on those elements of Claims 1, 7, and 18 of the '802 Patent.

Defendant disputes the injection site hemolysis element of Claim 1. Claim 1 claims that administration of the composition reduces injection site hemolysis relative to administration of a composition that does not include magnesium. (PTX-1.) The ANDA label does not explicitly discuss injection site hemolysis. (PTX-042.) Defendant argues that Plaintiffs' experiments cannot justify any improvements in hemolysis because the experiments were done on rabbit red blood cells, not humans.

(Dkt. 250 at 26; Dkt. 254 at 12–13.) Defendant contends that an experiment conducted on non-human subjects cannot prove that hemolysis will be reduced in Plaintiffs' product designed for human use, much less prove that Defendant's ANDA product will reduce hemolysis in human subjects. (Dkt. 250 at 26.) Defendant also argues that Plaintiffs' tests did not truly show reduced injection site hemolysis relative to a composition that does not include magnesium. (*Id.* at 26–27.) And Defendant finds fault in Dr. Friedman's "say-so" testimony about his experience and observations of hemolysis in his patients because Dr. Friedman did not corroborate that testimony with any documentation. (*Id.* at 27; Dkt. 254 at 12–13.)

But, as with the osmolality element of the '105 Patent, injection site hemolysis reduction is a property of both Minocin and the ANDA label. It is not a specific step that a physician who administers either product must do before injecting it into a patient; instead, hemolysis reduction is a beneficial property that all patients who receive the products will experience. As with osmolality, that the ANDA product is meant to reduce hemolysis is not explicitly stated on the product label. But what is clear from the label is that it has a higher pH and a lower injection volume. A POSA reading that label would understand that if an intravenous formulation has a pH that is too low, it would cause irritation, pain, and other tolerability issues to the patient. As such, a POSA would immediately know that a high pH and low injection volume would mean reduced hemolysis for the patient in comparison to the prior art minocycline with its lower pH and higher injection volume. This alone means that a

physician following Defendant's ANDA instructions would directly infringe on the injection hemolysis element of Claim 1 of the '802 Patent.

As to Defendant's argument about the lack of comparator human trials, such trials would be cost prohibitive and would inappropriately put patients at harm because prior art minocycline had known issues. (Dkt. 249 at 21.) Nor did the FDA require such trials. The FDA approved Minocin as an improvement over the prior art minocycline based on the existing data presented by the inventors showing an improvement in hemolysis reduction as compared to the prior art minocycline. The FDA only required clinical human trials if Plaintiffs were seeking to change the side effect warnings on the label—information called "class labeling" that appears on all formulations of all tetracyclines. Because Plaintiffs did not set out to do this, human clinical trials were not necessary.

Plaintiffs instead appropriately relied on substantial experimental data from in vitro and in vivo studies directly measuring the incidence of injection site hemolysis. These studies showed that the composition in the '802 Patent reduces the risk of injection site hemolysis in comparison to a formulation with magnesium. (*See* PTX-1; PTX-087; PTX-196.) All experiments tested aqueous solutions with minocycline and magnesium at varying molar ratios and pH levels against the prior art minocycline formulation. The experiments were conducted on mice and human endothelial cells (not injected directly into human veins), but that does not make the experiments less useful. Conducting this type of experiment on humans would have come with a higher risk of harm to any volunteer receiving the prior art minocycline,

which had known tolerability issues. And, as several experts testified, the models used in these experiments are well-known to be reliable methods to evaluate injection site hemolysis in humans because the models study the same cell types that would be damaged in human injection site hemolysis. Because these experiments showed reduced injection site hemolysis in the claimed invention versus the prior art minocycline, it was appropriate for Plaintiffs and the FDA to rely on them. These experiments provide adequate support for the injection site hemolysis reduction element of Claim 1.

Dr. Friedman, who has extensive experience administering intravenous minocycline to patients to treat bacterial infections, also testified that he no longer uses the prior art minocycline because Minocin significantly reduces tolerability issues. Both of Defendant's expert witnesses, Dr. Klibanov and Dr. Chambers, admitted that they do not have any experience administering minocycline to patients intravenously. Dr. Friedman's real-world experience thus weighs heavily in support of Plaintiffs' argument that its product reduces the incidence of hemolysis.

Based on this evidence, the Court holds that a POSA administering the ANDA product would infringe on the injection site hemolysis element of Claim 1 of the '802 Patent. Plaintiffs can justify its injection site hemolysis reduction claim with the experiments it conducted and Dr. Friedman's testimony. And at bottom, the ANDA label, even though it does not explicitly mention hemolysis, will inevitably lead physicians to directly infringe on the hemolysis reduction claim.

2. Defendant is Liable for Induced Infringement.

Induced infringement occurs when an alleged infringer actively induces direct infringement by another party. 35 U.S.C. § 271(b) ("Whoever actively induces infringement of a patent shall be liable as an infringer."). The patent holder must establish "first that there has been direct infringement, and second that the alleged infringer knowingly induced infringement and possessed specific intent to encourage another's infringement." *Minn. Mining & Mfg. Co. v. Chemque, Inc.*, 303 F.3d 1294, 1304–05 (Fed. Cir. 2002). But, in pharmaceutical cases, the "mere existence of direct infringement by physicians, while necessary to find liability for induced infringement, is not sufficient" for induced infringement. *Takeda Pharms. U.S.A., Inc. v. W.-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015.) A plaintiff must prove specific intent, knowledge, and action to induce infringement. *Id.* (citing *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1364 (Fed. Cir. 2003)).

The "knowledge" element of induced infringement requires "knowledge of the existence of the patent that is infringed" and "knowledge that the induced acts constitute patent infringement." *Global-Tech Appliances, Inc. v. SEB S.A.*, 563 U.S. 754, 765 (2011); *see also Commil USA, LLC v. Cisco Sys., Inc.*, 575 U.S. 632, 639 (2015). An alleged infringer possesses the requisite intent to induce infringement when there is "[e]vidence of active steps taken to encourage infringement, such as advertising an infringing use or instructing how to engage in an infringing use." *Metro-Goldwyn-Mayer Studios Inc. v. Grokster, Ltd.*, 545 U.S. 913, 915 (2005). These actions show "an affirmative intent that the product be used to infringe," thus constituting induced infringement. *Id.*

In pharmaceutical patent cases, the label or instructions on an ANDA can be evidence of an intent to induce infringement. Evidence that the ANDA's labeling or instructions "would inevitably lead some physicians to infringe" would "establish[] the requisite intent for inducement." *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1369 (Fed. Cir. 2017). *See also Sanofi v. Watson Lab'ys Inc.*, 875 F.3d 636, 644–45 (Fed. Cir. 2017) ("inferred intent" to induce infringement present because defendant's proposed labels encouraged physicians to prescribe the medication, knowing that such a prescription would be infringement); *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010) ("The pertinent question is whether the proposed label instructs users to perform the patented method. If so, the proposed label may provide evidence of [defendant's] affirmative intent to induce infringement."); *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1329 n.2 (Fed. Cir. 2009) ("The question is not, however, whether a user following the instruments may end up using the device in an infringing way. Rather it is whether [the defendant's] instructions teach an infringing use of the device such that we are willing to infer from those instructions an affirmative intent to infringe the patent.").

Defendant argues that it did not induce infringement of the osmolality and hemolysis elements in the patents-in-suit because the ANDA product label mentions neither. (Dkt. 250 at 22–25, 27–30; Dkt. 254 at 16–22.) Accordingly, Defendant argues, it cannot possibly encourage or instruct a POSA to infringe on those claim elements. (*Id.*) But, as stated earlier, the Court's infringement analysis does not begin and end with the product label. Infringement of claim elements can occur when the

ANDA label encourages the claimed administration of the product, even when what is claimed is not explicitly stated on the ANDA label. And because both osmolality of less than 500 mOsmol/kg and reduced injection site hemolysis are properties of the patents-in-suits' composition that inevitably result from the proper administration of the composition, a POSA following the identical ANDA label will also inevitably administer a formulation with osmolality less than 500 mOsmol/kg and reduced injection site hemolysis. Accordingly, because Defendant's label will encourage and instruct a POSA to administer the ANDA product in a way that infringes the patents-in-suit, the Court infers Defendant's knowledge and affirmative intent to infringe the patents-in-suit.

In addition, as to the hemolysis reduction claim element of the '802 Patent, Plaintiffs presented evidence of Defendant's knowledge that its ANDA product would infringe when Defendant submitted its ANDA to the FDA. Defendant, in its submission, explicitly stated at multiple times that the function of magnesium in its product was to reduce injection site hemolysis. Dr. deVries testified to this, and Defendant did not dispute it. Defendant's affirmative statements to the FDA that its ANDA product would reduce injection site hemolysis is additional evidence that Defendant had knowledge that its product would infringe. Accordingly, the Court finds that Defendant induced infringement of the disputed claim elements.

3. Defendant Is Liable for Contributory Infringement.

Contributory infringement occurs when the alleged infringer sells a material component of a patented invention for practicing a patented process, and the material

component has no substantial noninfringing use. 35 U.S.C. § 271(c) ("Whoever . . . sells within the United States . . . component of a patented machine, manufacture, combination or composition, or a material or apparatus for use in practicing a patented process, constituting a material part of the invention, knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial non-infringing use, shall be liable as a contributory infringer."). Therefore, a contributory infringement action succeeds if four elements are proven: (1) there is direct infringement; (2) the accused infringer had knowledge of the patent; (3) the component had no substantial non-infringing use; and (4) the component is a material part of the invention. *Fujitsu Ltd. V. Netgear Inc.*, 620 F.3d 1321, 1326 (Fed. Cir. 2010).

The "knowledge" element requires that the alleged infringer have had knowledge both that the component was patented, and that the use of it would be infringing. *Commil*, 575 U.S. at 639; *Fujitsu*, 620 F.3d at 1330. Whether a use is considered "substantial" is often the key inquiry. A component has no "substantial" non-infringing use if it is not "unusual, far-fetched, illusory, impractical, occasional, aberrant, or experimental." *Vita-Mix Corp.*, 581 F.3d at 1327. A court considers "not only the use's frequency, but also the use's practicability, the invention's intended purpose, and the intended market" in assessing whether an asserted non-infringing use was "substantial." *i4i Ltd. P'ship v. Microsoft Corp.*, 598 F.3d 831, 851 (Fed. Cir. 2010).

Defendant argues it is not liable for contributory infringement because it did not have knowledge of infringement, and because Plaintiffs cannot prove direct infringement. (Dkt. 250 at 22–23, 27–28.) But Plaintiffs have proven direct infringement, and the Court has found that Defendant had the requisite knowledge of infringement. There is no dispute as to the fourth element of contributory infringement, regarding whether the ANDA product is a material part of the invention, because the ANDA product is identical to the invention in the patents-in-suit.

Defendant argues that as to the third element of contributory infringement, Plaintiff failed to show no "substantial" non-infringing use because some of the injection volumes and pH levels allowed by the ANDA label are outside of the claim elements. (*Id.* at 18–19.) But those injection volumes and pH levels would be, as Dr. deVries and Dr. Friedman testified, outside the standard of care for any POSA administering the product. It would be highly unusual, unsafe, and unlikely for a POSA to administer the ANDA product outside of the measurements within the claim elements. Accordingly, the injection volumes and pH levels that fall outside the claim elements are not "substantial" for purposes of contributory infringement. The purpose for which the ANDA product is to be used is to treat bacterial infections, and a POSA following the ANDA label to treat bacterial infections will administer the ANDA product in a way that meets all of the disputed claim elements. In other words, there is no substantial non-infringing use for the ANDA product. Defendant is also liable for contributory infringement.

B. Invalidity—Obviousness

A patent is invalid for obviousness when the nature of the differences between the claimed invention and the prior art would have rendered the subject matter of the invention obvious to a POSA. 35 U.S.C. § 103 ("A patent for a claimed invention may not be obtained . . . if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains."). The party seeking to invalidate a patent based on obviousness "must demonstrate 'by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.' " *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007)).

Defendant argues that Minocin was an obvious invention because a POSA would have been motivated to combine three prior art references (the prior art minocycline product, CN'268, and Gibbs) to achieve the claimed invention with a reasonable likelihood of success. (Dkt. 250; Dkt. 254.) Plaintiffs argue that Defendant has not met its burden to show obviousness by clear and convincing evidence, and they present several secondary considerations of non-obviousness. (Dkts. 249; 251.)

1. A POSA Would Not Have Been Motivated to Combine the Prior Art Minocycline, CN'268, and Gibbs to Achieve the Claimed Invention with a Reasonable Likelihood of Success.

A court may find a motivation to combine prior art references by looking to (1) teachings in prior art, (2) the common sense of a POSA, or (3) any need or problem known to a POSA that would be addressed by the claimed invention. *Plantronics, Inc. v. Aliph, Inc.*, 724 F.3d 1343, 1354 (Fed. Cir. 2013). But when analyzing a motivation to combine, a court must be careful to not base motivation on hindsight or reading the invention's teachings into the prior art. *See, e.g.*, *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 36 (1966) (Courts must "resist the temptation to read into the prior art the teachings of the invention in issue."); *Grain Processing Corp. v. Am. Maize-Prods. Co.*, 840 F.2d 902, 907 (Fed. Cir. 1988) (quoting *Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1012 (Fed. Cir. 1983)) ("Care must be taken to avoid hindsight reconstruction by using 'the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.' ").

A "reasonable expectation of success" does not require an absolute expectation of success, just that the prior art have at least provided some indication of "which parameters are critical" and "which of many possible choices is likely to be successful." *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009) (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)). In summary, when there is a "design need or market pressure to solve a problem" and "a finite number of identified, predictable solutions," a POSA has reason to pursue known options to solve that problem. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007). If pursuing those options "leads to

the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense" and therefore is obvious. *Id.*

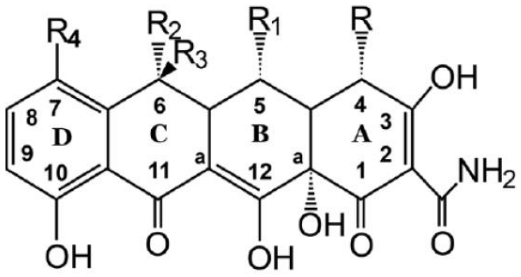
The extent of Defendant's obviousness argument hangs on three prior art references: the prior art minocycline, CN'268, and Gibbs. Defendant argues that these three prior art references would have motivated a POSA to improve the prior art minocycline by adding magnesium at a higher molar ratio to minocycline and would have reasonably expected to be successful in doing so. Defendant first argues that the prior art minocycline product taught that minocycline treated bacterial infections caused by the Acinetobacter bacteria using a formulation of minocycline reconstituted in 5 mL of water and then further diluted in 500–1,000 mL of a diluent. Defendant then argues that CN'268 taught that the addition of magnesium to a parenteral doxycycline formulation would improve solubility, stability, and tolerability, and this teaching could be extended to minocycline. Finally, Defendant argues that Gibbs taught that adding magnesium to tetracyclines at a molar ratio of up to 8:1 would improve a formulation. Defendant contends that these prior art references are very similar to the claims at issue in this case because they generally taught that the addition of magnesium to tetracyclines could improve the pH, and because doxycycline and minocycline can be used interchangeably because they have similar chemical structures.

But there are significant differences between these three prior art references and Minocin that Defendant fails properly to account for. As to the first prior art reference, it is true that the prior art minocycline teaches a minocycline formulation

to treat bacterial infections. But the prior art minocycline teaches a formulation with a much lower reconstituted pH of 2.0 to 2.8. Minocin teaches a minocycline formulation that adds magnesium to achieve a higher reconstituted pH. Defendant argues that the prior art minocycline does teach a higher pH covered by the patents-in-suit when the prior art minocycline is diluted with Lactated Ringer's. This argument is of no matter because the Court has defined the pH levels in the patents-in-suit to refer to the reconstituted solution, not the diluted solution. But even if the Court did agree with Defendant's proposed construction, the higher pH of Lactated Ringer's stated in the prior art minocycline label is still not covered by the claims at issue because, as Dr. Friedman testified, that diluent is not within the standard of care for intravenous administrations and would be considered inappropriate for intravenous use by a POSA.

As to the other two prior art references Defendant cites, CN'268 and Gibbs, a POSA would not have been motivated to combine them with the prior art minocycline product to achieve the claimed invention. CN'268 and Gibbs contain several important differences from Minocin. First, both concern doxycycline formulations, not minocycline formulations. Second, both disclose only intramuscular formulations, not intravenous formulations. Third, both teach the addition of a surfactant, dissolvent, or antioxidant to improve solubility and stability. Fourth, neither mention hemolysis or the significance of an increased molar ratio of magnesium to minocycline. The Court will address each of these differences in turn.

First, the Court cannot agree with Defendant that a POSA would be motivated to extrapolate findings in CN'268 and Gibbs about doxycycline to minocycline. Even though the two tetracyclines share structural similarities, there are sufficient differences between the two. The parties agree that minocycline and doxycycline share a chemical structure made up of four fused rings as shown in the figure below.



The parties also agree that minocycline and doxycycline differ in the upper rings (notated by the letter R) but have the same bottom rings. They agree that magnesium binds to the lower rings. Defendant uses this similarity to argue that because magnesium binds to the lower rings in both doxycycline and minocycline, a POSA could extrapolate findings about a magnesium-doxycycline formulation to a magnesium-minocycline formulation.

But it is not that simple. Defendant relies on the Nelson reference to support its argument that magnesium binds with doxycycline and minocycline at the exact same location. But Defendant fails to mention that Nelson also teaches that the upper region of the two tetracyclines is also implicated when binding with a metal cation like magnesium. When the upper regions are different, as they are in doxycycline and minocycline, the two compounds can act in dramatically different ways when they interact with magnesium. Dr. deVries testified to this fact, and Dr. Klibanov also

agreed that small structural differences in two similar compounds can nevertheless lead to significant differences in how the compounds interact with metal cations.

In addition, Dr. Friedman, the only witness who had any experience administering and treating patients with minocycline, testified credibly that minocycline was specifically effective against the Acinetobacter bacteria. Defendant also agreed that minocycline was more effective than doxycycline against this particular bacteria, which Minocin is intended to treat.

Defendant also argues that the Gibbs reference confirms the relevance of doxycycline formulations to minocycline formulations because Gibbs represents that the two can be used interchangeably. But, as Dr. deVries testified, and Defendant does not dispute, Gibbs does not provide any data on minocycline formulations. The entirety of Gibbs discusses and provides examples and experiments on doxycycline formulations, not minocycline formulations.

Second, both CN'268 and Gibbs disclose intramuscular formulations, not intravenous formulations. Defendant argues that findings on intramuscular formulations can be extrapolated to intravenous formulation because the only difference between the two is the injection site: a muscle versus a vein. But, as Dr. deVries testified, there are more differences than just the injection site. Importantly, an intramuscular formulation can be injected into the muscle without being a fully aqueous solution. But an intravenous formulation cannot be injected into the vein unless it is fully solubilized, meaning all components must be dissolved. Full solubility is, therefore, extremely important for an intravenous formulation such as

what is described in the patents-in-suit. Accordingly, two intramuscular formulations studied by CN'268 and Gibbs would not have been helpful to a POSA because they do not necessarily require complete solubility.

Relatedly, to improve solubility in the CN'268 and Gibbs intramuscular formulations, both discuss the addition of a solubilizing agent such as oil to improve the solubility of both formulations. But the patents-in-suit do not allow for the addition of a solubilizing agent. And to improve stability, CN'268 and Gibbs discuss the addition of a stabilizing agent. Neither discusses that magnesium would have any effect, much less a positive effect, on stability and solubility in the doxycycline formulations that they studied. A POSA would thus understand that CN'268 and Gibbs teach that adding solubilizing and stabilizing agents are necessary to improve stability and solubility for doxycycline formulations. They would not, as Defendant argues, learn from these prior art references that magnesium could improve solubility and stability in a minocycline formulation.

Finally, neither CN'268 nor Gibbs discusses anything about reduced injection site hemolysis or the significance of a high molar ratio of magnesium to minocycline. Defendant points out that Gibbs teaches a formulation in molar ratios up to 8:1, which overlaps with the claimed 4:1 range. But, as Plaintiffs counter, Gibbs does not teach anything about the significance of a higher molar ratio, thus not teaching a POSA to create a formulation with a higher magnesium-minocycline ratio. And CN'268 teaches nothing about a higher molar ratio; instead, it teaches the opposite ratio than the molar ratio that is claimed. CN'268 teaches an excess of doxycycline to

magnesium—the opposite of the claimed excess of magnesium to minocycline. Thus, neither CN'268 nor Gibbs would motivate a POSA to combine magnesium with the prior art minocycline at a high molar ratio of magnesium to minocycline.

Defendant makes brief references to a handful of additional prior art references to support their arguments. But these references suffer from the same faults as CN'268 and Gibbs—they only study doxycycline, they discuss intramuscular formulations, and they require the addition of stabilizing and solubilizing agents.

Accordingly, for these reasons, Defendant has not shown by clear and convincing evidence that a POSA would have been motivated to combine the prior art minocycline, CN'268, and Gibbs to create the claimed invention. Even if a POSA was so motivated, the POSA would not have a reasonable expectation of success. First, doxycycline and minocycline are similar compounds with similar structures, but they have important differences, especially in how they respond to magnesium binding. Second, CN'268 and Gibbs teach very different formulations than the claimed invention. A POSA would not be motivated to extrapolate findings about doxycycline-based intramuscular formulations to a minocycline-based intravenous formulation. The claims at issue are thus not obvious.

2. Secondary Considerations

Plaintiffs' evidence of secondary considerations support this Court's finding that the Asserted Claims are not obvious. A party attempting to refute an assertion of obviousness may present objective evidence of non-obviousness (also referred to as "secondary considerations") such as (1) commercial success, (2) long-felt but unmet

need, (3) failure of others to solve the problem, (4) unexpected results created by the claimed invention, (5) prior art teaching away, and (6) copying. *See Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc.*, 711 F.3d 1348, 1368 (Fed. Cir. 2013). These objective considerations are important because they counteract any potential prejudice of hindsight bias. *See id.* In fact, they may often be the "most probative and cogent evidence in the record," because secondary considerations may "establish that an invention appearing to have been obvious in light of the prior art was not." *Apple Inc.*, 839 F.3d at 1052–53 (quoting *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538–39 (Fed. Cir. 1983)). Secondary considerations must be considered as part of all the evidence, and "not just when the decisionmaker remains in doubt after reviewing the art." *Id.* Evidence of non-obviousness through secondary considerations does not, however, necessarily overcome a strong prima facie showing of obviousness. *Asyst Techs., Inc.*, 544 F.3d at 1316.

(a) Prior Art Taught Away from the Patents-in-Suit.

The initial secondary consideration Plaintiffs offer is that prior art taught away from the claimed invention. Prior art "may be said to teach away when a person of ordinary skill, upon reading the [prior art], would be discouraged from following the path set out . . . or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

Plaintiffs presented five prior art references that teach away from the claimed invention. Dr. deVries testified about each reference in detail. Defendant's experts provided limited testimony in response to these references.

First, the deVries 2006 reference teaches away from the claimed invention in the patents-in-suit. The deVries 2006 reference studied a formulation of minocycline and magnesium at a molar ratio of up to 3:1 with an increased pH. DeVries's experiments consistently resulted in minocycline precipitating out of solution and becoming insoluble, making it unsuitable and dangerous for intravenous administration. This reference taught away from the claimed invention because it would teach a POSA that any minocycline-magnesium formulation formulated with a molar ratio of greater than 3:1 would be expected to be insoluble. Defendant argues in its post-trial briefing (neither expert testified about deVries 2006) that deVries 2006 was irrelevant to a POSA because it studies oral formulations. True enough, but those oral formulations were aqueous solutions, making them more suitable for comparison to the claimed invention, which is also an aqueous solution. Thus, deVries 2006 still teaches a POSA to not mix magnesium and minocycline at a molar ratio higher than 3:1 if the POSA wants to create a safe aqueous solution.

Second, the Barringer 1974 reference teaches away from the claimed invention for the same reason deVries 2006 does—magnesium-minocycline formulations become insoluble at a molar ratio higher than 2:1. Dr. Klibanov testified that Barringer was irrelevant to a POSA because it discussed oral absorption. But Dr. Klibanov also testified that Barringer relevantly taught that adding magnesium to minocycline in aqueous solutions causes insolubility and precipitation, which is relevant to whether such a solution would be suitable for intravenous administration.

Third, the Berthon 1983 and Allen 1967 references teach away from the claimed invention because they teach that the solubility of minocycline decreases when mixed with magnesium and an increased pH. These references would teach a POSA to avoid mixing magnesium with minocycline at a higher pH because it would not lead to a suitable soluble intravenous formulation.

Fourth, the Pawelczyk 1982 reference teaches away from the claimed invention because it teaches that minocycline is more stable at a lower pH and begins to degrade at a pH around 4. Pawelczyk also teaches that the addition of magnesium does nothing to improve stability of minocycline in aqueous solutions in comparison to aqueous minocycline solutions without magnesium. Accordingly, the Pawelczyk reference teaches a POSA that a minocycline formulation with a higher pH would be unstable, and the addition of magnesium would not do anything to improve stability.

These prior art references thus teach away from the claimed invention. They teach that a magnesium-minocycline formulation at a higher molar ratio and a higher pH level would not result in a stable and soluble formulation. But the patents-in-suit found the opposite—a magnesium-minocycline formulation at a molar ratio of greater than 4:1 would result in a soluble and stable formulation at a higher pH.

(b) Plaintiffs Presented Evidence of Unexpected Results.

Evidence of unexpected results includes evidence that the new invention contains a combination of known elements that resulted in superior and unexpected properties as compared to the prior art. *See, e.g.*, *Procter & Gamble Co.*, 566 F.3d at 997–98. Unexpected results are also important to a showing of non-obviousness

because the fact that the results were unexpected means that a POSA would not have had a reasonable expectation of success. *See Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1309 (Fed. Cir. 2010).

The prior art references discussed above taught an avoidance of adding magnesium to minocycline at a molar ratio of 3:1 because it would lead to solubility and stability problems. But the inventors of the patents-in-suit found that a molar ratio of greater than 3:1 could successfully create an aqueous solution suitable for intravenous administration at a higher pH and a lower volume of administration. These were unexpected results in the light of the prior art which taught away from these results, and these unexpected results were a clear improvement over the prior art minocycline.

(c) The Claimed Invention Met a Long-Felt But Unmet Need.

Evidence of a long-felt but unmet need that was met by the new invention is important to a showing of non-obviousness because it shows that if there was a need for a solution to a problem for a long time that took a long time to resolve, the eventual resolution was likely not obvious. *See Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1380 (Fed. Cir. 2006).

The prior art minocycline was first published in 1973 and never substantively changed until Minocin was approved in 2015. A POSA knew that the prior art minocycline had solubility and stability problems requiring it to be administered at a lower pH and a higher injection volume. A POSA also knew that low pH levels caused irritability and injection site hemolysis. These issues made the prior art

minocycline highly unfavored for use in treating bacterial infections, as Dr. Friedman testified. Attempts to improve the solution were unsuccessful and ran into similar solubility and stability problems.

Minocin successfully solved these solubility and stability problems because of the addition of magnesium at a higher molar ratio. This addition enabled the formulation to be administered a higher and more tolerable pH level and a lower injection volume, which led to reduced tolerability and injection site hemolysis issues. Dr. Friedman, who has treated numerous patients with Minocin and no longer uses the prior art minocycline at all, testified that Minocin resolved all the solubility and stability issues that came with the prior art minocycline. Defendant's experts, who have never administered minocycline, disagreed at first but later agreed that the addition of magnesium in Minocin improves solubility and stability.

Thus, the prior art minocycline's shortcomings presented a need for improvement, a need that was unmet for over forty years until Minocin entered the market.

(d) Plaintiffs Presented Evidence that Defendant Copied Minocin, But Copying Is Required in Hatch-Waxman Litigation.

Evidence that the alleged infringer copied the invention can be a secondary consideration of non-obviousness, because a presumption exists that a POSA would have tried to obtain the same results as the invention but without copying. *See WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1336 (Fed. Cir. 2016). In Hatch-Waxman pharmaceutical cases, however, evidence of copying is often not probative because "a showing of bioequivalence is required for FDA approval" in those cases. *Bayer*

Healthcare Pharms., Inc. v. Watson Pharms., Inc., 713 F.3d 1369, 1377 (Fed. Cir. 2013).

Plaintiffs argue that because Defendant chose to copy the Minocin product instead of the prior art minocycline product, this choice shows that Defendant knew the Minocin product had some benefit over the prior art minocycline. This choice thus points to non-obviousness, according to Plaintiffs. It may be true that Defendant chose to copy Minocin over the prior art minocycline because Defendant believed that Minocin had benefits that the prior art minocycline did not have. But such copying is less persuasive evidence of non-obviousness in Hatch-Waxman litigation, because the FDA requires that an ANDA product be the exact same as the patented product, so copying is necessary.

C. Section 112 Invalidity Defenses

Defendant asserts that indefiniteness, lack of written description, and lack of written enablement render the patents-in-suit invalid. Section 112 requires patent specifications to distinctly define the subject matter of the patent, contain a written description of the invention, and contain an explanation on the manner and process of using the invention. 35 U.S.C. § 112. Failure of a patent to satisfy these requirements may render the patent invalid. *See Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336 (Fed. Cir. 2010).

1. Indefiniteness

An inventor must distinctly claim the subject matter of the invention in the patent claims. 35 U.S.C. § 112(b) ("The specification shall conclude with one or more

claims particularly pointing out and distinctly claiming the subject matter which the inventor . . . regards as the invention."). A patent that fails to do so may be invalid for indefiniteness. Specifically, a patent is "invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014).

Defendant argues that Claims 1, 7, and 18 of the '802 Patent are invalid for indefiniteness because each claim requires that injection site hemolysis be reduced as compared to a formulation without magnesium, but the '802 Patent does not define injection site hemolysis or instruct how to measure it. Because, according to Defendant, the claim term creates a "zone of uncertainty," the '802 Patent claims are invalid for indefiniteness. (Dkt. 250 at 56.)

Defendant's indefiniteness argument appears to the Court to be the same argument it made about the term "injection site hemolysis" in its claim construction briefings, an issue the Court has resolved in a previous Part of this Memorandum. The term "injection site hemolysis" is now properly construed, so Defendant's indefiniteness argument is moot. The '802 Patent is not invalid for indefiniteness.

2. Lack of Enablement and Lack of Written Description.

Defendant argues that all Asserted Claims in both patents-in-suit are invalid for lack of written description and lack of enablement. Specifically, Defendant argues that the Asserted Claims are invalid for (1) the injection site hemolysis reduction claim (Claims 1, 7, and 18 of the '802 Patent); (2) the pH limitations (Claims 1 and 18

of the '802 Patent, and Claim 27 of the '105 Patent); (3) the claimed volume range (Claim 18 of the '802 Patent); and (4) the osmolality range (Claim 27 of the '105 Patent).

A patent that fails to include a specification with sufficient specificity such that a POSA can use the invention without too much experimentation based on that specification may be invalid for lack of enablement. 35 U.S.C. § 112(a) ("The specification shall contain . . . the manner and process of making and using [the invention], in such full, clear, concise, and exact terms as to enable any person skilled in the art . . . to make and use the same . . . ."). The accused infringer can successfully hold a patent invalid for lack of enablement by showing that a POSA would not be able to use the claimed invention "without undue experimentation." *In re Wands*, 858 F.2d 731, 736–37 (Fed. Cir. 1988).

Some experimentation, of course, is permissible. A specification does not need to "describe with particularity how to make and use every single embodiment within a claimed class" and is not inadequate "just because it leaves the skilled artist to engage in some measure of adaptation or testing." *Amgen Inc. v. Sanofi*, 598 U.S. 594, 610–11 (2023). A "reasonable amount of experimentation to make and use a patented invention" is expected and will not invalidate the patent. *Id.* at 612. What counts as "reasonable" in any patent case "will depend on the nature of the invention and the underlying art." *Id.* The question is whether the amount of experimentation required will "detract from the basic statutory requirement that a patent's specification describe the invention 'in such full, clear, concise, and exact terms as to enable any

person skilled in the art' to 'make and use' the invention." *Id.* (quoting 35 U.S.C. § 112(a)).

A patent's specification that fails to provide a sufficient written description may leave the patent invalid for lack of written description. 35 U.S.C. § 112(a) ("The specification shall contain a written description of the invention."). This written description "must 'clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.' " *Ariad Pharms., Inc.*, 598 F.3d at 1351 (quoting *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1562–63 (Fed. Cir. 1991)). The test for sufficiency of the written description is "whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Id.* The written description in the specification must accurately represent the scope of the patent, not broadening or overreaching the actual scope of the invention. *Id.* at 1353–54.

Defendant first argues that the pH claim elements are invalid for lack of written description and lack of enablement because under some conditions that fall within the scope of the claims, a POSA would not be able to make formulations at some of the claimed pH levels because they would become insoluble and thus unsuitable for intravenous administration. Next, Defendant argues that the osmolality and volume claim elements are invalid for lack of enablement and written description because neither specify a lower limit. According to Defendant, administering the formulation at an osmolality of 0 mOsmol/kg (which would fit

within the claim term of "less than about 500 mOsmol/kg") or at a volume of 1 mL (which would fit within the claim term of "less than 500 mL") would be dangerous and unsuitable for intravenous administration. But Defendant's expert witnesses also testified that a POSA would be able to adjust the intravenous formulation such that it would be administered at an appropriate and safe pH level, osmolality, and injection volume. A POSA would know the appropriate and safe ranges for each element and would adjust them accordingly to ensure that the administered formulation was not insoluble, toxic, or intolerable for the patient. A POSA would never administer—or even consider administering—a drug at a dangerously low osmolality or pH, or a dangerously high injection volume. A POSA would not need to do an unduly amount of experimentation to discover what the appropriate pH, osmolality, and volume should be. A POSA would be able to understand the purpose of the invention and how to use it effectively. Accordingly, the patents-in-suit are not invalid for lack of written description or for lack of enablement.

VI. CONCLUSION

Based on the foregoing findings of fact and conclusions of law, the Court concludes that Plaintiffs have shown by a preponderance of the evidence that Defendant has infringed on the '105 Patent and the '802 Patent, and that Defendant has failed to show by clear and convincing evidence that the Asserted Claims of the patents-in-suit are invalid for obviousness, indefiniteness, lack of written description, or lack of enablement. Accordingly, the Court finds that the Asserted Claims of the

'802 Patent and the '105 Patent are valid and enforceable and thus enters judgment in favor of Plaintiffs Melinta and against Defendant Nexus.[14]

SO ORDERED in No. 21-cv-02636.

Date: November 15, 2024

JOHN F. KNESS
United States District Judge

[14] For the reasons set forth in this Memorandum, the Court finds for Plaintiffs. But Plaintiffs' litigation position was not so strong, nor was the manner in which Defendant litigated so unreasonable, as to justify this being an "exceptional" case. Accordingly, Plaintiffs are not entitled to an award of reasonable attorneys' fees under 35 U.S.C. § 285. *See Octane Fitness, LLC v. ICON Health & Fitness, Inc.*, 572 U.S. 545, 554 (2014) ("an 'exceptional' case is simply one that stands out from others with respect to the substantive strength of a party's litigating position (considering both the governing law and the facts of the case) or the unreasonable manner in which the case was litigated.").